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B081041

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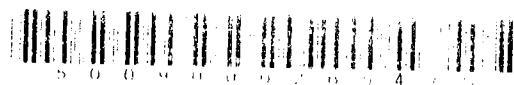
**FINAL REPORT**

A 28-Day Repeated Dose Oral Toxicity Study of [REDACTED] C B I [REDACTED] in Rats

(Study No. B081041)

Date: April 2, 2009

C B I



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*TEST DATA*

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**1. Statement**

Sponsor: [REDACTED] CBI [REDACTED]

Title: A 28-Day Repeated Dose Oral Toxicity Study of [REDACTED] CBI [REDACTED] in Rats

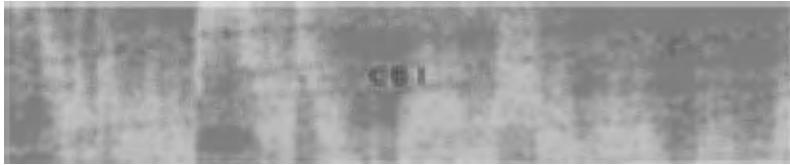
Study number: B081041

This study was conducted in compliance with the following Good Laboratory Practice Standards.

Standards Concerning Testing Facilities Implementing Studies Related to New Chemical Substances



Study director: Signed and sealed Date: April 2, 2009



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Quality Assurance Statement

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**3. Study Outline**

**3.1 Title**

A 28-Day Repeated Dose Oral Toxicity Study of [REDACTED] CBI [REDACTED] in Rats

**3.2 Study number**

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**3.3 Purpose**

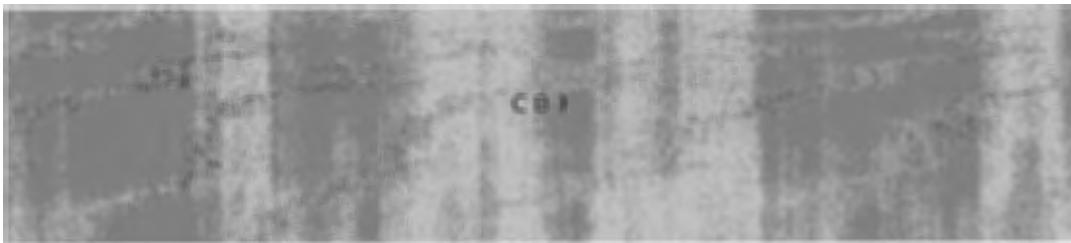
The purpose of this study was to assess the potential toxic effects of [REDACTED] CBI [REDACTED] and its reversibility by observing functional and morphological changes after a 28-day repeated oral administration of [REDACTED] CBI [REDACTED] to rats.

**3.4 Guideline**

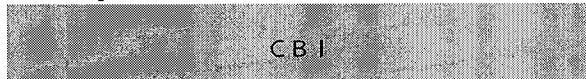
Testing Method Concerning Designated Chemical Substances



**3.5 GLP**



**3.6 Sponsor**



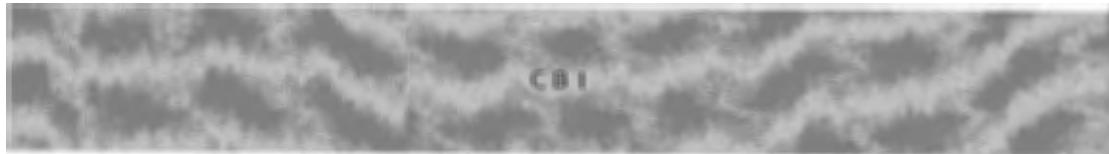
**3.7 Organization under contract**



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**3.8 Test facility**



**3.9 Study director**

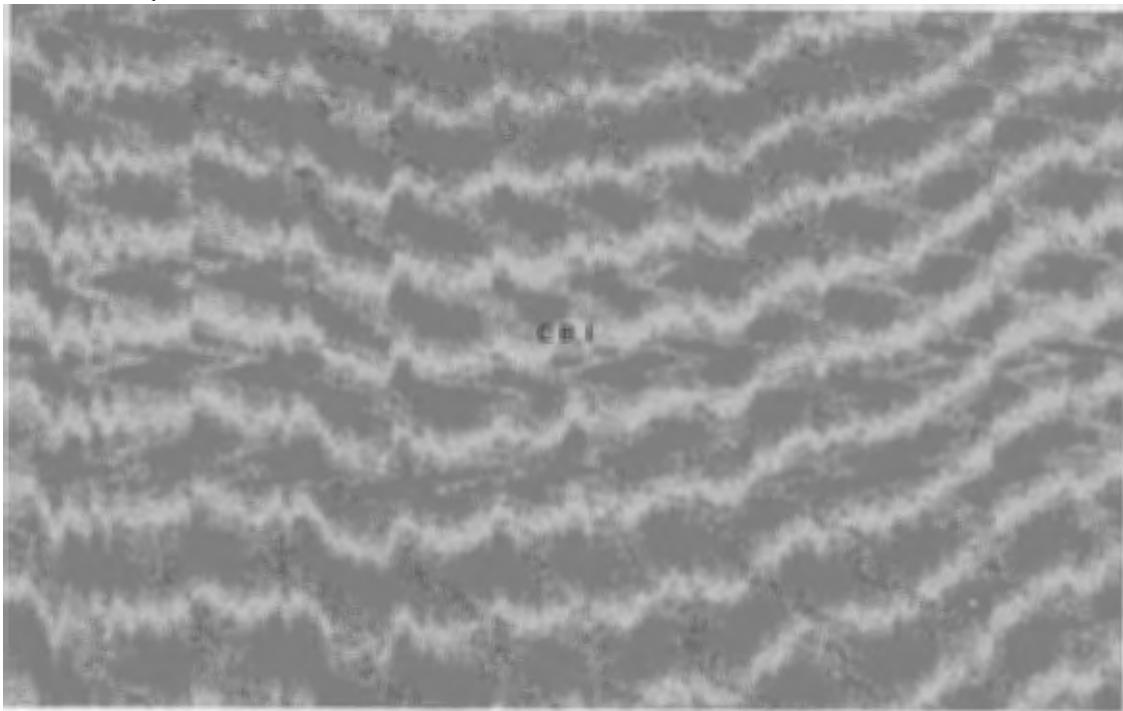


**3.10 Principal scientists**

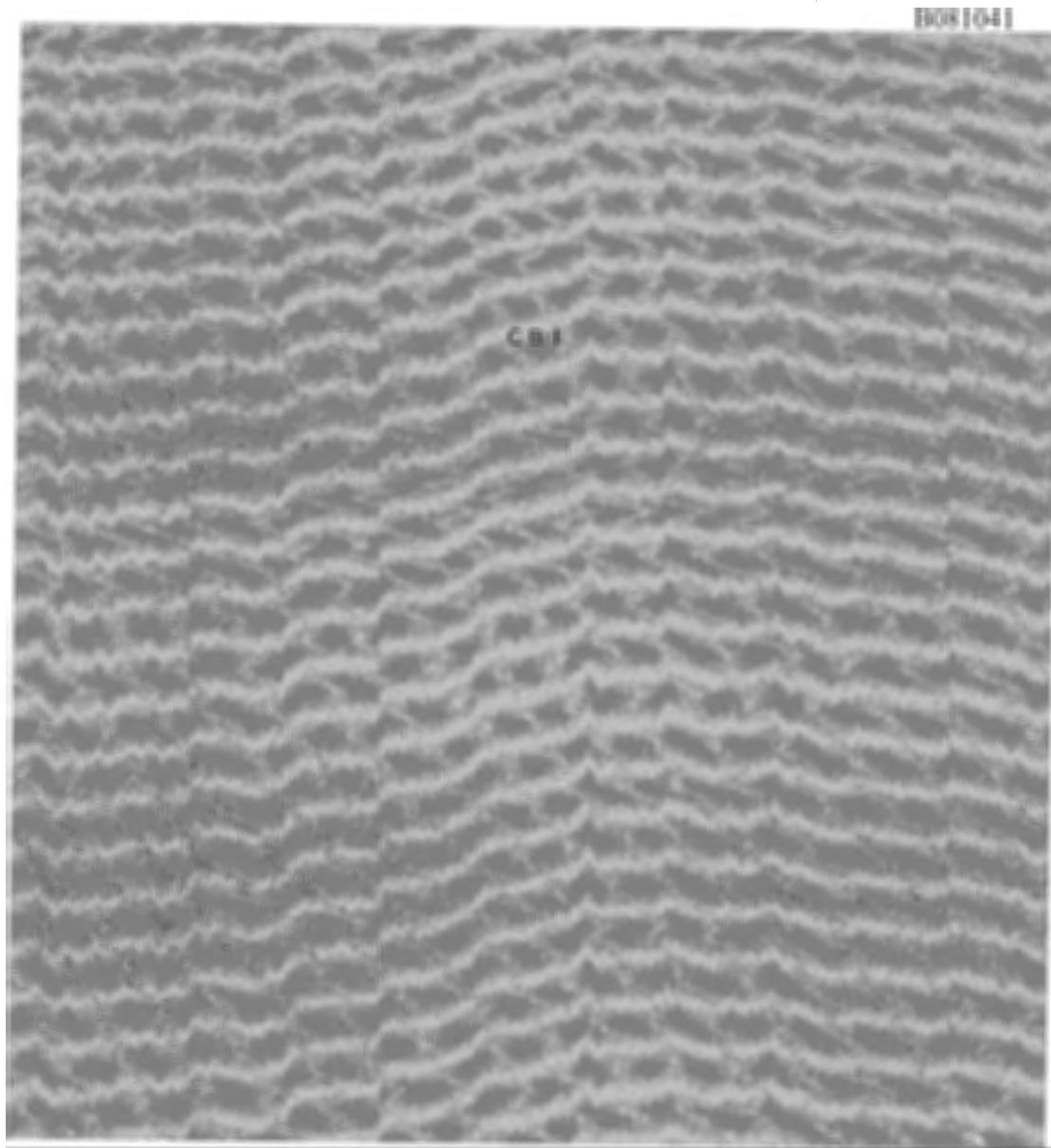
- Test substance analysis
- Clinical examination
- Pathology



**3.11 Study contributors**



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### **3.12 Study schedule**

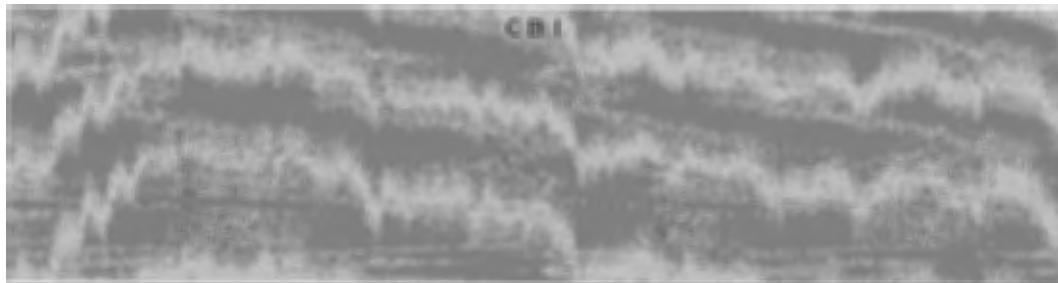
Initiation of the study	October 21, 2008
Initiation of experiment (Animal receipt)	October 22, 2008
Initiation of administration	October 28, 2008
Necropsy after the dosing period	November 25, 2008
Necropsy after the recovery period	December 9, 2008

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Completion of experiment (Shipment of the specimens)	February 9, 2009
Completion of the study	April 2, 2009

### **3.13 Retention**



### **3.14 Retention materials**

- (1) Protocol
- (2) Protocol amendment
- (3) Test substance
- (4) Test substance records
- (5) Test animal records
- (6) Study result records
- (7) Correspondence documents
- (8) Specimens
- (9) Final report

### **3.15 Ethics**

The study protocol was reviewed and approved by the [REDACTED]

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**4. Study Director Signature**

Sponsor:

C B I

Title: A 28-Day Repeated Dose Oral Toxicity Study of [REDACTED] C B I [REDACTED] in Rats

Study number: B081041

Study director: Signed and sealed Date: April 2, 2009



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### 5. Summary

█ C B I █ was repeatedly administered by oral gavage at dose levels of 0, 0.5, 5, and 50 mg/kg/day to male and female Crl:CD(SD) rats (SPF) for 28 days to assess the toxicological effects of █ C B I █ and its reversibility by observing functional and morphological changes.

The body weight and food consumption decreased in males at 50 mg/kg/day.

In the hematology, red blood cell count, hemoglobin concentration, and hematocrit decreased in males of all test substance-treated groups and females at 50 mg/kg/day. MCHC decreased in males at 5 and 50 mg/kg/day and females at 50 mg/kg/day. MCH decreased and platelet count increased in males at 50 mg/kg/day. PT was prolonged in males of all test substance-treated groups and APTT was prolonged in females at 50 mg/kg/day.

In the blood chemistry, A/G ratio increased in males of all test substance-treated groups and females at 50 mg/kg/day. Albumin increased in males at 5 and 50 mg/kg/day and females at 50 mg/kg/day. Total protein increased in males at 5 mg/kg/day and females at 50 mg/kg/day. Urea nitrogen and glucose increased in males of all test substance-treated groups. ALP and total bilirubin increased in males at 5 and 50 mg/kg/day. ALAT increased in males and females at 50 mg/kg/day. Triglyceride decreased as well as ASAT and chlorine increased in males at 50 mg/kg/day. At the end of the recovery period, total cholesterol increased in males at 50 mg/kg/day.

In the liver, an increased liver weight, enlargement and brownish change of the liver at necropsy, and centrilobular hypertrophy of hepatocytes in the histopathology were noted in males of all test substance-treated groups and females at 50 mg/kg/day.

In addition, whitish patch of the liver was noted in males at 5 and 50 mg/kg/day at necropsy. Focal necrosis of hepatocytes was noted histopathologically in males of all test substance-treated groups and females at 50 mg/kg/day. Granuloma and focal brown pigment (hemosiderin) deposition of the macrophages were noted in males at 50 mg/kg/day. At the end of the recovery period, focal proliferation of the bile duct was noted in males at 50 mg/kg/day.

In the thyroid, increased thyroid weight was noted in males at 50 mg/kg/day. Hypertrophy of the follicular cells was noted histopathologically in males of all test substance-treated groups and females at 50 mg/kg/day.

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In the adrenal, diffuse hypertrophy of the glomerulosa cells was noted in males of all test substance-treated groups and females at 50 mg/kg/day. At the end of the recovery period, adrenal weight increased in males at 50 mg/kg/day.

The reversibility of the following changes was not observed after the 2-week recovery period; hypertrophy of the thyroid follicular cells in both sexes, diffuse hypertrophy of the glomerulosa cells of the adrenal in both sexes, increases in serum total protein, albumin, and total cholesterol in males, focal proliferation of the bile duct of the liver in males, increase in adrenal weight in males, and prolongation of APTT in females. The reversibility of the other changes was observed.

No treatment-related abnormalities were noted in the clinical observations, detailed clinical observations, function tests, or urinalysis.

Consequently, the no-observed-effect-level (NOEL) of [ CBI ] was considered to be less than 0.5 mg/kg/day for males and 5 mg/kg/day for females under the conditions of this study.

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**6. Materials and Methods**

**6.1 Test substance**

**6.1.1 IUPAC name**

CBI

**6.1.2 Byname (abbreviation)**

CBI

**6.1.3 Lot No.**

CBI

**6.1.4 Purity**

99.3%

**6.1.5 Impurities and their concentrations**

CBI

**6.1.6 Appearance at normal temperatures**

White powder

**6.1.7 Supplier**

CBI

**6.1.8 Storage conditions**

The test substance was stored at room temperature (actual range: 16.3° to 21.4°C, permissible range: 10° to 30°C) under light-resistant and well-closed conditions.

**6.1.9 Storage area**

The test substance storage area 41

**6.1.10 Stability**

Infrared absorption spectrum of the test substance was measured by infrared absorption spectrometry (IR spectrometry: tablet method) before and after the dosing period at the test facility. Based on the results, the stability of the test substance used in this study

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was confirmed (see Section 11.1).

Analytical instrument: [REDACTED] C B I  
[REDACTED] C B I [REDACTED]

### 6.1.11 Handling of residual test substance

Residual test substance was returned to the sponsor upon completion of the study except for about 2 g for retention.

### 6.1.12 Safety precautions

Safety glasses, a mask, and rubber gloves were worn.

## 6.2 Vehicle

### 6.2.1 Name

Purified water

It was prepared with Elix-5 (Millipore Corporation) on each day of preparation of the dosing solutions.

## 6.3 Experimental animals

### 6.3.1 Species

Rat

### 6.3.2 Strain

Crl:CD(SD)

### 6.3.3 Rationale for strain selection

This strain is widely used in toxicity studies using rodents, and there is abundant historical data and a large number of animals are available.

### 6.3.4 Microbial level

SPF

### 6.3.5 Supplier

[REDACTED] C B I [REDACTED]

### 6.3.6 Number of animals purchased

32 animals of each sex

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**6.3.7 Quarantine and acclimation**

A quarantine period (from animal receipt to the final day of quarantine) was set for 5 days. All animals were observed once daily with respect to health condition during this period and were confirmed to be in good health. Their body weights were measured on the day of receipt and the final day of quarantine period to confirm that there were no abnormalities in individual body weight gain. An acclimation period (from animal receipt to the start of dosing) was set for 6 days. All animals were observed once daily during this period. In addition, detailed clinical observations were performed once after grouping on the day before the start of dosing (see Section 6.10.2). Consequently, no abnormalities were noted in any animal.

**6.3.8 Age at the start of dosing**

5 weeks old

**6.3.9 Body weights at the start of dosing**

Body weights ranged from 146 to 168 g in males and 122 to 145 g in females. It was confirmed that the body weight of each animal was within the mean body weight  $\pm$  20%.

**6.3.10 Grouping**

All animals were confirmed to be in good health based on their clinical signs and body weights during the quarantine and acclimation periods. The animals were assigned to the groups by stratified-by-weight randomization method on the day before the start of dosing to give homogeneous distribution of the body weight among the groups. Thirty animals of each sex were subjected to this study.

**6.3.11 Identification**

Before the grouping, animals were identified by oil-based ink marks on their tails, and the cages were identified by labels listing the study number, cage numbers, quarantine/acclimation animal numbers, animal species, strain, and sex. After the grouping, animals were implanted subcutaneously with transponders registered animal numbers into their back and were identified using a microchip reader [REDACTED] C B I [REDACTED]

[REDACTED] C B I [REDACTED] Cages were identified with labels listing the study number, test substance name, group name (dose level), animal numbers, animal species, strain, and sex. During the detailed clinical observations and function tests (excluding measurement of motor activity), the above labels were removed and temporary labels were attached to the cages, to blind the observers from the dose levels and original animal numbers. A corresponding table of the identification and animal numbers was also prepared. Surplus animals were identified using quarantine/acclimation animal numbers

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at the detailed clinical observations during the acclimation period.

#### **6.3.12 Disposition of surplus animals**

The surplus animals were excluded from the study on the day after the initial administration and were transferred to another preliminary study (study number B080403) in order to utilize the animals efficiently.

### **6.4 Animal management**

#### **6.4.1 Animal room**

Animal rooms for rat and mouse (during quarantine: No. 4125, after quarantine: No. 2121)

#### **6.4.2 Environmental control**

##### **6.4.2.1 Room temperature**

Room No. 4125: 21.2° to 22.1°C (permissible range: 19.0° to 25.0°C)

Room No. 2121: 20.8° to 22.4°C (permissible range: 19.0° to 25.0°C)

##### **6.4.2.2 Relative humidity**

Room No. 4125: 45.9% to 58.1 % (permissible range: 35.0% to 75.0%)

Room No. 2121: 47.1% to 59.2% (permissible range: 35.0% to 75.0%)

##### **6.4.2.3 Ventilation**

6 to 20 changes per hour with all fresh filtered air

##### **6.4.2.4 Lighting period**

12 hours per day (7:00 to 19:00)

#### **6.4.3 Animal accommodation**

##### **6.4.3.1 Cage**

Autoclaved hanging type stainless steel wire mesh cages (195W × 325D × 180H mm; [REDACTED] C B I [REDACTED] were used and replaced on the day of grouping and once every 2 weeks after the start of dosing.

##### **6.4.3.2 Feeder**

Autoclaved stainless steel feeders for pellet diet [REDACTED] C B I [REDACTED] were used and replaced on the day of grouping and once a week after the start of dosing.

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**6.4.3.3 Water delivery system**

Automatic water delivery system [REDACTED] C B I [REDACTED]

**6.4.3.4 Rack**

Autoclaved stainless steel racks equipped with an automatic water delivery system [REDACTED] C B I [REDACTED] were used and replaced on the day of grouping and once every 2 weeks after the start of dosing.

**6.4.3.5 Tray**

Autoclaved aluminum trays [REDACTED] C B I [REDACTED] were used and replaced on the day of grouping and once a week after the start of dosing. Hardwood chips for experimental animals [REDACTED] C B I [REDACTED] were placed on the trays and were replaced at the same time as the trays.

**6.4.4 Diet**

**6.4.4.1 Description**

Pellet diet for experimental animals irradiated by radioactive rays [REDACTED] C B I [REDACTED]

C B I [REDACTED]

**6.4.4.2 Feeding**

Diet was given *ad libitum* except during the measurement of motor activity and fresh urine collection and was replaced at the same time as the feeders. The animals were fasted from the evening before the scheduled necropsy for more than 16 hours (about 21 to 23 hours).

**6.4.4.3 Analysis**

Analysis data [REDACTED] C B I [REDACTED]

[REDACTED] C B I [REDACTED] On the basis of the analysis data, it was confirmed that the levels of the environmental contaminants, such as residual pesticides in the lots used in this study were all within the permissible levels of the Standard Operating Procedure of the test facility.

**6.4.5 Water supply**

**6.4.5.1 Description**

Tap water passed through a 5- $\mu\text{m}$  filter and disinfected by UV irradiation

**6.4.5.2 Watering**

Water was given *ad libitum* except during the measurement of motor activity and fresh

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urine collection.

**6.4.5.3 Analysis**

Tap water is periodically analyzed by [REDACTED] C B I [REDACTED] twice a year. From the analytical data, it was confirmed that the quality of the water met the specifications of the Standard Operating Procedure of the test facility.

**6.4.6 Number of animals per cage**

One animal per cage

**6.5 Administration**

**6.5.1 Route and method**

Oral (by gavage)

The test substance was administered orally using a disposable syringe attached to a gastric tube.

**6.5.2 Frequency and period**

Once daily (8:01 to 10:48) for 28 days

**6.5.3 Rationale for administration conditions**

In accordance with the guideline "Testing Method Concerning Designated Chemical Substances"

**6.5.4 Dose level and its rationale**

0.5, 5, and 50 mg/kg/day

In a study entitled "7-day repeated dose oral toxicity study of [REDACTED] C B I [REDACTED] in rats" (study No.: B081043, dose levels: 0, 50, 100, and 250 mg/kg, 5 males and females for each group) conducted by the test facility, an increase in A/G ratio in the blood chemistry, an increase in liver weight in the organ weight measurement, and enlargement of the liver at necropsy were noted in both sexes at 50 mg/kg/day and higher. Inhibition of body weight gain, decreases in hemoglobin concentration and hematocrit in the hematology, increases in ALAT(GPT), ALP, urea nitrogen, glucose, albumin as well as decreases in total cholesterol and triglyceride in the blood chemistry, and whitish patches of the liver at necropsy were noted in males at 50 mg/kg/day and higher.

Based on the results, the highest dose for this study was set at 50 mg/kg/day, at which obvious toxicity changes were expected, and lower dose levels were set at 5 and 0.5 mg/kg/day. Additionally, a control group (0 mg/kg/day) receiving the vehicle (purified water) alone was also set.

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**6.5.5 Dose volume**

The dose volume was set at 10 mL/kg and the individual volume was calculated on the basis of the most recently measured body weights.

**6.6 Preparation of dosing solutions**

**6.6.1 Method and frequency**

Dosing solutions were prepared once within 8 days under UV-cut fluorescent light.

Weighed test substance was dissolved in purified water to make a 5 mg/mL dosing solution using a measuring cylinder. This solution was diluted with purified water to make 0.05 and 0.5 mg/mL dosing solutions using measuring cylinders.

The dosing solutions were divided into brown glass bottles for each dosing day and stored in a refrigerator (actual range: 3.5° to 6.1°C, permissible range: 1° to 10°C) under light-resistant conditions for no longer than 8 days after preparation.

**6.6.2 Stability**

The test substance in the dosing solutions was confirmed to be stable at 0.02 and 100 mg/mL for 8 days under refrigeration and shielded from light in a well-closed container in a study entitled "Validation of the Analytical Method for [REDACTED] Concentration in Preparation (Study No. B080579)" conducted at the test facility.

The results are shown below.

Nominal conc. (mg/mL)		The day of preparation (Initial)	8 days after preparation
0.02	Measured conc. (mg/mL)	0.0198 0.0199 0.0197	0.0200 0.0200 0.0203
	Mean	0.0198	0.0201
	SD	0.000010	0.000017
	CV(%)	0.5	0.8
Ratio to initial concentration (%)		-	101.5
100	Measured conc. (mg/mL)	98.8 98.1 98.9	99.2 99.2 99.5
	Mean	98.6	99.3
	SD	0.44	0.17
	CV(%)	0.4	0.2
Ratio to initial concentration (%)		-	100.7

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### 6.6.3 Confirmation of concentrations

The dosing solutions of the initial preparation were analyzed ( $n=2$ ) by the method described in Section 6.7 and the mean concentration of each dosing solution was within the nominal concentration  $\pm 10\%$ . The results are shown below.

Nominal conc. (mg/mL)	Measured conc. (mg/mL)	Mean (mg/mL)	Ratio to nominal conc. (%)
0.05	0.0500 0.0495	0.0498	99.6
0.5	0.495 0.494	0.495	99.0
5	4.97 5.05	5.01	100.2

## 6.7 Analytical method of dosing solution

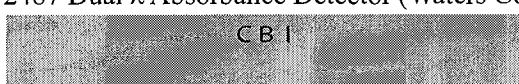
The dosing solutions were analyzed in accordance with an analytical method validated at the test facility (study No. B080579).

### 6.7.1 Analytical conditions

#### 6.7.1.1 HPLC operating conditions

HPLC system: 2695 Separations Module (Waters Corporation)  
Detector: 2487 Dual  $\lambda$  Absorbance Detector (Waters Corporation)

Column:



Column temperature: 40°C

Mobile phase:  
A: 0.6% Perchloric acid/Acetonitrile (1:1, v/v)  
B: Acetonitrile

Flow rate:

Time (min)	Flow (mL)	%A	%B
0.00	1.0	100	0
12.00	1.0	100	0
12.01	1.5	0	100
17.00	1.5	0	100
17.01	1.0	100	0
25.00	1.0	100	0

Detection: UV 210 nm

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Injection volume: 50 µL  
Auto-injector temperature: 25°C  
Auto-injector washing: Acetonitrile/Water (1:1, v/v)

### 6.7.1.2 Preparation of standard solutions

Standard solutions were prepared according to the following table (ST-1, ST-2, and ST-3, n=1).

Standard solution	Preparation method		Concentration (µg/mL)
SS-1	C B I	ca. 20 mg → 20 mL/methanol	1000
SS-2	SS-1, 1 mL	→ 10 mL/methanol	100
ST-1	SS-2, 1 mL	→ 10 mL/purified water	10
ST-2	SS-2, 2 mL	→ 10 mL/purified water	20
ST-3	SS-2, 4 mL	→ 10 mL/purified water	40

### 6.7.2 Preparation of sample solutions

Sample solutions were prepared according to the following table (n=2).

Dosing solution (mg/mL)	Preparation method	Solution code	Concentration (µg/mL)
0.05	Dosing suspension, 2 mL → 5 mL/purified water	A	20
0.5	Dosing suspension, 1 mL → 25 mL/purified water	B	20
5	Dosing suspension, 1 mL → 25 mL/purified water	C	200
	Solution C, 1 mL → 10 mL/purified water	D	20

### 6.7.3 HPLC measurement

#### (1) Analysis of standard solutions

The standard solutions (ST-1, ST-2, and ST-3) were injected into the HPLC set to the conditions described in Section 6.7.1. From the resulting peak areas and the concentrations of C B I in the standard solutions, a calibration curve was established and the equation for the linear regression line was calculated.

#### (2) Analysis of sample solutions

The sample solutions were injected into the HPLC set to the conditions described in Section 6.7.1. The C B I concentration was calculated from the peak area, equation for the linear regression of the calibration curve, and dilution factor.

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### 6.8 Recovery period

Five males and females each in the control and 50 mg/kg/day groups were subjected to the recovery period of 14 days after the end of the dosing period.

### 6.9 Study design

Group	Conc. (mg/mL)	Necropsy after dosing period <sup>*2</sup>		Necropsy after recovery period <sup>*3</sup>	
		Male	Female	Male	Female
Control <sup>*1</sup>	0	5 <sup>*4</sup> (20101-20105) <sup>*5</sup>	5 (60101-60105)	5 (20106-20110)	5 (60106-60110)
0.5 mg/kg	0.05	5 (20201-20205)	5 (60201-60205)	-	-
5 mg/kg	0.5	5 (20301-20305)	5 (60301-60305)	-	-
50 mg/kg	5	5 (20401-20405)	5 (60401-60405)	5 (20406-20410)	5 (60406-60410)

\*1, Treated with the vehicle; \*2, Necropsy on the day after the final dosing (Day 29);

\*3, Necropsy on the day after the recovery period (Day 43); \*4, Number of animals;

\*5, Animal No.

### 6.10 Observations and measurements

The following parameters were examined. The first day of dosing was designated as Day 1, and Days 1 to 7 were designated as Week 1. Moreover, Day 29 and later was designated as the recovery period.

#### 6.10.1 Clinical observation

All animals were observed twice a day (before and after dosing) during the dosing period, and once a day in the morning during the other period.

#### 6.10.2 Detailed clinical observations

The following parameters were examined once before the start of dosing and once a week in the afternoon (following the clinical observation after dosing) during the dosing period. The following hand-held observations and open field observations for a 2-min period were performed. The observations during the recovery period were not performed since no treatment-related effects were noted during the dosing period. At the examinations, animals were identified with temporary animal numbers to blind the observers from the dose levels and original animal numbers. Criteria of each parameter are shown in Section 11.2.

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### [Hand-held observations]

Reactivity on removal from the cage, reactivity to handling, aggression, skin (trauma, color of skin), fur (soiled fur), eyes (exophthalmos, palpebral closure), mucous (color of conjunctiva), secretion, lacrimation, salivation, piloerection, pupil size

### [Open field observations]

Rearing, arousal, urination, defecation, posture/body position, breathing, co-ordination movement, gait, tremor, clonic convulsion, tonic convulsion, stereotypy, bizarre behavior

#### **6.10.3 Function tests**

The following parameters were examined once in the afternoon (following the observation after dosing) in the final dosing week (Week 4). Sensory reactivity to stimuli was observed, followed by a measurement of grip strength. Grip strength was measured twice for each animal using a digital force gauge [REDACTED] C B I [REDACTED], and a higher value was applied. Motor activity was recorded for 1 hour using a motor activity-measuring device [REDACTED] C B I [REDACTED]. Data were calculated every 10 minutes from the start of the measurement, while a total of 1 hour was calculated. For the measurement of motor activity, animals were acclimated to polycarbonate cages (with bedding) after observation following dosing. Animals were transferred to new cages at the time of measurement. Moreover, the animals were deprived of food and water during the measurements. For measurements except for the motor activity, animals were identified with temporary animal numbers to blind the observers from the dose levels and original animal numbers. The tests during the recovery period were not performed since no treatment-related effects were noted during the dosing period.

### [Sensory reactivity to stimuli]

Approach response, touch response, auditory response, tail pinch response, aerial righting reaction

\* Criteria of each parameter are shown in Section 11.2.

### [Grip strength]

Grip strength of forelimb and hindlimb

### [Motor activity]

#### **6.10.4 Body weights**

All animals were weighed on Days 1, 8, 15, 22, and 28 during the dosing period and on Days 29, 36, and 42 during the recovery period using electronic balances [REDACTED] C B I [REDACTED] C B I [REDACTED]. The measurements during the dosing period were conducted

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before dosing.

**6.10.5 Food consumption**

Gross weight of each feeder was weighed using an electronic balance [ CBI ] [ CBI ]. Mean daily food consumption values during Days 1 to 8, 8 to 15, 15 to 22, 22 to 26, 29 to 36, and 36 to 40 were calculated. The mean daily food consumption for each period is expressed with the data of the last day of each period.

**6.10.6 Hematology**

Hematological examinations were performed at the scheduled necropsy (Days 29 and 43). All animals were fasted from the evening on the day before the examinations (for about 21 to 23 hours). Blood samples were obtained from the inferior vena cava under anesthesia with intraperitoneal injection of sodium thiopental [ CBI ]. The following parameters were measured using the obtained blood. Each blood sample anticoagulated with 3.2 w/v% trisodium citrate solution was centrifuged at 12,000 rpm, 12,100 g, at 4°C for 3 minutes, and parameters 9 and 10 were examined using the obtained plasma. The other parameters were examined using each blood sample anticoagulated with EDTA-2K. The residual samples were discarded after termination of the examinations.

Parameter	Method
1 Red blood cell count	Hydrodynamic focusing DC detection method
2 Hemoglobin concentration	SLS-hemoglobin method
3 Hematocrit	RBC pulse wave-height detection method
4 Mean corpuscular volume (MCV)	Calculated from 1 and 3
5 Mean corpuscular hemoglobin (MCH)	Calculated from 1 and 2
6 Mean corpuscular hemoglobin concentration (MCHC)	Calculated from 2 and 3
7 Reticulocyte ratio (%)	Flow cytometry with semi-conductor laser
8 Platelet count	Hydrodynamic focusing DC detection method
9 Prothrombin time (PT)	Scattered light detection method
10 Activated partial thromboplastin time (APTT)	Scattered light detection method
11 Leukocyte count	Flow cytometry with semi-conductor laser
12 Differential leukocyte count (%)	Flow cytometry with semi-conductor laser

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Measuring instruments:

1 to 3, 7, 8, 11, and 12; [REDACTED]

C B I

9 and 10; [REDACTED]

C B I

**6.10.7 Blood chemistry**

A portion of the collected blood samples at the scheduled necropsy (Days 29 and 43) was left to stand at room temperature for more than 30 minutes, and then serum was separated by centrifugation at 3,000 rpm, 1,600 g, at 4°C for 10 minutes for the following parameters. The remaining serum was stored in a freezer set at -20°C (permissible range: -15°C or below) and discarded by the completion of this study.

Parameter	Method
1 ASAT (GOT)	UV-rate method [REDACTED] C B I [REDACTED]
2 ALAT (GPT)	UV-rate method [REDACTED] C B I [REDACTED]
3 $\gamma$ GT	L- $\gamma$ -Glutamyl-3-carboxy-4-nitroanilid substrate method [REDACTED] C B I [REDACTED] [REDACTED] C B I [REDACTED]
4 ALP	p-Nitrophenylphosphate substrate method [REDACTED] C B I [REDACTED] [REDACTED] C B I [REDACTED]
5 Total bilirubin	Enzymatic method (BOD method)
6 Urea nitrogen	Enzymatic-UV method (Urease-LEDH method)
7 Creatinine	Enzymatic method (Creatininase-POD method)
8 Glucose	Enzymatic method (HK-G6PDH method)
9 Total cholesterol	Enzymatic method (CO-HMMPS method)
10 Triglyceride	Enzymatic method (GPO-HMMPS method with elimination of glycerol)
11 Total protein	Biuret method
12 Albumin	BCG method
13 A/G ratio	Calculated from 11 and 12
14 Calcium	OCPC method
15 Inorganic phosphorus	Enzymatic method (PNP-XOD-POD method)
16 Sodium (Na)	Ion-selective electrode method
17 Potassium (K)	Ion-selective electrode method
18 Chlorine (Cl)	Ion-selective electrode method

Measuring instrument: [REDACTED]

C B I

**6.10.8 Urinalysis**

Fresh urine samples were collected using metabolic cages from 5 males and females in each group (in ascending order of animal numbers) in the final week of the dosing period

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(Day 26) and the following parameters were examined. Animals were deprived of food and water during fresh urine sampling.

According to the result, no abnormalities were detected in any parameters; therefore, the examination was terminated. The residual samples were discarded after the termination of the examination.

Parameter	Method	
1 pH	Paper test	C B I
2 Protein	Paper test	C B I
3 Glucose	Paper test	C B I
4 Ketones	Paper test	C B I
5 Occult blood	Paper test	C B I

Measuring instrument: C B I

### **6.10.9 Pathological examination**

#### **6.10.9.1 Organ weights**

The following organs from all animals were weighed using an electronic balance C B I. Bilateral organs were weighed together, and thyroids were weighed after fixation with 10 vol% neutral phosphate-buffered formalin.

Body weights were measured on the day of necropsy and were used to calculate the relative organ weights (ratio to body weight).

Liver, kidneys, adrenals, testes, epididymides, ovaries, thymus, spleen, brain, heart, thyroids

#### **6.10.9.2 Necropsy**

All animals were euthanized after the blood sampling by exsanguination from the abdominal aorta and then subjected to necropsy.

#### **6.10.9.3 Histopathology**

The following organs/tissues of all animals were removed and fixed in 10 vol% neutral phosphate-buffered formalin except that the testes were fixed in Bouin's solution and the eyeballs were fixed in Davidson's solution. All organs/tissues were preserved in 10 vol% neutral phosphate-buffered formalin.

Brain (including cerebrum, cerebellum, and pons), spinal cord, stomach, duodenum, jejunum, ileum (including Payer's patch), cecum, colon, rectum, liver, kidneys, adrenals, spleen, heart, thymus, eyeballs, pituitary, thyroids (including parathyroids), urinary bladder, trachea, lungs, testes, epididymides, prostate, ovaries, uterus, mandibular

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lymphnode, mesenteric lymphonode, sciatic nerve (right), bone marrow (femur, right), gross lesions

The above-mentioned organs/tissues of all males and all females in the control and 50 mg/kg/day groups at the end of the dosing period and gross lesions noted in all groups were processed by the standard method to prepare hematoxylin and eosin-stained sections and were examined by microscopy (eyeballs: specimen was prepared and examined unilaterally [right]). The parathyroid of 1 female each (#60102 and #60402) in the control and 50 mg/kg/day groups was examined unilaterally. Consequently, the treatment-related changes were noted at 50 mg/kg/day in the liver, thyroids, and adrenals. Therefore, these organs were examined for all males and all females at the end of the dosing and recovery periods. In addition, Berlin blue-stained sections of the liver were prepared and examined microscopically in 2 males (#20402 and #20403) at 50 mg/kg/day since hemosiderin deposition was suspected.

#### **6.10.10 Shipment of the specimens**

Paraffin blocks of the liver, pancreas, testis, and kidney and 7 unstained sections of the thyroid were prepared from each animal and sent to the sponsor.

The paraffin block of each organ was prepared from the area not subjected to (or the area with no possibility of) the histopathological examination. The paraffin block of the pancreas was prepared from the area connected to the digestive tract.

#### **6.11 Statistical analysis**

Numerical data of multiple groups were analyzed for their statistical significance by multiple comparison tests. Homogeneity of variance among the groups was first tested by Bartlett's test. If the group variance was determined to be homogeneous, all groups were compared by one-way analysis variance. If Bartlett's test indicated heterogeneous variance, Kruskal-Wallis test was employed, and Dunnett (if homogeneous) or Dunnett type (if heterogeneous) multiple comparison test was used when there was a significant difference between the groups. The numerical data of recovery animals were analyzed by F test. If the variance was homogenous, t test was applied. If the variance was heterogeneous, Welch's test was applied.

The categorical data of multiple groups concerning the urinalysis were analyzed by Kruskal-Wallis test. Dunnett type multiple comparison test was used when there was a significant difference between the groups. The categorical data of histopathology were analyzed by Wilcoxon's rank sum test for each finding between the control and each treatment group.

The significant level of 5% was set for Bartlett's test, one-way analysis variance, and

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Kruskal-Wallis test. The significant levels of 1% and 5% were set for the other analyses. Toxicological Data Processing System [REDACTED] C B I was used for analyses.

Statistical analysis was performed on items listed below. The analysis was not performed on clinical signs, detailed clinical observations (except for rearing), function tests (approach response, touch response, auditory response, tail pinch response, aerial righting reaction), or necropsy findings.

### [Numerical data]

Detailed clinical observation (rearing), function tests (grip strength of forelimb and hindlimb, motor activity), body weight, food consumption, hematology, blood chemistry, absolute organ weights, relative organ weights

### [Categorical data]

Urinalysis (pH, protein, glucose, ketones, occult blood), histopathological examination

### **6.12 Computer system**

Toxicological Data Processing System [REDACTED] C B I was used to collect and analyze the data indicated below. The scope and schedule of data collection, etc., were registered for the applicable computer system protocol. B081041\_ ( indicates a blank space) was used as the computer system protocol number.

(1) Grouping, calculation of dosing volume

(2) On-line data collection

Clinical signs, body weights, food consumption, hematology, blood chemistry, urinalysis (pH, protein, glucose, ketone, occult blood), organ weights, histopathological examination

(3) Off-line data collection

Detailed clinical observation, function tests, necropsy

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## **7. Results**

### **7.1 Clinical signs**

The data are shown in Table 1 and Appendices 1 and 2.

No abnormalities were noted in any animals.

### **7.2 Detailed clinical observations**

The data are shown in Tables 2 to 6 and Appendices 3 to 7.

No abnormalities were noted in any animals.

### **7.3 Function tests**

The data are shown in Figure 1, Tables 7 and 8, and Appendices 8 and 9.

No treatment-related changes were noted in any animals.

A statistically significant low value of the motor activity was noted in females at 0.5 mg/kg/day at time 40 – 50 min after the start of the measurement, however, it was not considered to be treatment-related since there was no dose-correlation.

### **7.4 Body weights**

The data are shown in Figure 2, Table 9, and Appendix 10.

A statistically significant low value of the body weight was noted in males at 50 mg/kg/day on Days 15 to 36 during the dosing and recovery periods. This change was not noted at the end of the recovery period.

### **7.5 Food consumption**

The data are shown in Table 10 and Appendix 11.

A statistically significant low value of the food consumption was noted in males at 50 mg/kg/day on Day 8 during the dosing period. This change was not noted from Day 15 onward.

### **7.6 Hematology**

The data are shown in Table 11 and Appendix 12.

At the end of the dosing period, statistically significant low values of red blood cell count, hemoglobin concentration, and hematocrit were noted in males of all test substance-treated groups. A statistically significant low value of MCHC was noted in males at 5 and 50 mg/kg/day. These changes were also noted in females at 50 mg/kg/day, but the low hematocrit value was not statistically significant. A statistically significant low value of MCH and a statistically significant high value of platelet count were noted in males at 50 mg/kg/day. Statistically significant prolongation of APTT was noted in females at 50 mg/kg/day. Prolongation of PT was

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noted in males of all test substance-treated groups, but this change was not statistically significant.

At the end of the recovery period, statistically significant prolongation of APTT was noted in females at 50 mg/kg/day. Statistically significant low values of red blood cell count, hemoglobin concentration, hematocrit, and MCHC were noted in males at 50 mg/kg/day, but the values of these parameters were higher than those at the end of the dosing period. A statistically significant high value of reticulocyte ratio was noted in males at 50 mg/kg/day but this change was not noted at the end of the dosing period.

In addition, statistically significant shortening of PT was noted in females at 50 mg/kg/day at the end of the dosing and recovery periods; however, it was not considered to be treatment-related since the individual values were within the normal range of the background data (see Section 11.3).

### 7.7 Blood chemistry

The data are shown in Table 12 and Appendix 13.

At the end of the dosing period, statistically significant high values of urea nitrogen, glucose, and A/G ratio were noted in males of all test substance-treated groups. Statistically significant high values of ALP, total bilirubin, and albumin were noted in males at 5 and 50 mg/kg/day. Statistically significant high values of ALAT and chlorine as well as a statistically significant low value of triglyceride were noted in males at 50 mg/kg/day. A statistically significant high value of total protein was noted in males at 5 mg/kg/day. A high value of ASAT was noted in 1 male (#20402) at 50 mg/kg/day. In females, statistically significant high values of ALAT, total protein, albumin, and A/G ratio were noted at 50 mg/kg/day.

At the end of the recovery period, statistically significant high values of total protein and albumin were noted in males at 50 mg/kg/day. A statistically significant high value of A/G ratio was noted in males and females at 50 mg/kg/day, but the values were lower than those at the end of the dosing period. A statistically significant high value of total cholesterol was noted in males at 50 mg/kg/day but this change was not noted at the end of the dosing period.

In addition, a statistically significant high value of calcium was noted in males at 50 mg/kg/day and statistically significant low values of ASAT and ALAT as well as a statistically significant high value of inorganic phosphorus were noted in females at 50 mg/kg/day at the end of the recovery period. However, these changes were not considered to be treatment-related since the individual values were within the normal range of the background data (see Section 11.3).

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**7.8 Urinalysis**

The data are shown in Table 13 and Appendix 14.

No abnormalities were noted in any animals at the final week of the dosing period.

**7.9 Organ weights**

The data are shown in Tables 14 and 15 and Appendices 15 and 16.

At the end of the dosing period, statistically significant high values of absolute and relative liver weights were noted in males of all test substance-treated groups and females at 50 mg/kg/day. A statistically significant high value of relative thyroid weight was noted in males at 50 mg/kg/day.

At the end of the recovery period, statistically significant high values of absolute and relative liver weights were noted in males and females at 50 mg/kg/day, but the values were lower than those at the end of the dosing period. A statistically significant high value of relative adrenal weight was noted in males at 50 mg/kg/day but this change was not noted at the end of the dosing period.

In addition, at the end of the dosing period, a statistically significant low value of absolute heart weight, and statistically significant high relative weights of the brain, kidneys, and testes were noted in males at 50 mg/kg/day. However, these changes were considered to be secondary since they resulted from the difference of body weight between the control and 50 mg/kg/day groups. A statistically significant low value of relative heart weight was noted in males at 0.5 mg/kg/day; however, it was not considered to be treatment-related since there was no dose-correlation.

**7.10 Necropsy**

The data are shown in Tables 16 and 17 and Appendix 17.

At the end of the dosing period, enlargement of the liver was noted in all males of all test substance-treated groups and all females at 50 mg/kg/day. Brownish change of the liver was noted in 1 male each at 0.5 and 5 mg/kg/day and all males and all females at 50 mg/kg/day. Whitish patch of the liver was noted in 1 male at 5 mg/kg/day and 3 males at 50 mg/kg/day.

At the end of the recovery period, enlargement of the liver was noted in all males and all females at 50 mg/kg/day. Whitish patch of the liver was noted in 2 males at 50 mg/kg/day.

In addition, at the end of the dosing period, unilateral defect and compensatory enlargement of the thyroid were noted in 2 females at 50 mg/kg/day; however, it was considered that the defect was congenital changes. Dilatation of the renal pelvis was

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noted in 1 male at 0.5 mg/kg/day; however, it was not dose dependent. Therefore, these changes were not considered to be treatment-related. At the end of the recovery period, asymmetry of the testes and a nodule of the thyroid were noted in 1 male at 50 mg/kg/day; however, these were not considered to be treatment-related since these changes were found in only 1 animal and were not noted at the end of the dosing period.

### 7.11 Histopathological examination

The data are shown in Tables 18 and 19 and Appendix 17, and Photographs 1 to 14. The treatment-related changes were noted in the liver, thyroid, and adrenal, and are summarized in the following text table.

Incidences of the treatment-related histopathological findings

Organ Findings	Period Sex Dose (mg/kg/day)	Week 5*								Week 7**			
		Male				Female				Male		Female	
		0	0.5	5	50	0	0.5	5	50	0	50	0	50
Liver		Grade											
	Hypertrophy, hepatocyte, centrilobular	1+	0	5	5	0	0	0	0	5	0	5	0
		2+	0	0	0	5	0	0	0	0	0	0	0
	Necrosis, hepatocyte, focal	1+	0	1	3	4	0	0	0	3	0	2	0
	Granuloma	2+	0	0	0	1	0	0	0	0	0	0	0
	Brown pigment deposition, macrophage, focal	1+	0	0	0	3	0	0	0	0	0	3	0
	Proliferation, bile duct, focal	1+	0	0	0	0	0	0	0	0	0	4	0
Thyroid		Grade											
	Hypertrophy, follicular cell	1+	0	1	2	3	0	0	0	3	0	3	0
Adrenal		Grade											
	Hypertrophy, glomerulosa cell, diffuse	1+	0	3	4	5	0	0	0	2	0	5	0

Grade: 1+, Minimal; 2+, Mild

\*, At the end of the dosing period; \*\*, At the end of the recovery period.

#### [At the end of the dosing period]

Liver: Centrilobular hypertrophy of hepatocytes was noted in all males of all test substance-treated groups and all females at 50 mg/kg/day. This change was statistically significant in males of all test substance-treated groups and females at 50 mg/kg/day. Eosinophilic granular change was noted in cytoplasm of the hypertrophied hepatocytes. Focal necrosis of hepatocytes was noted in 1 male at 0.5 mg/kg/day, 3 males at 5 mg/kg/day, and 4 males and 3 females at 50 mg/kg/day, and this change was statistically significant in males at 50 mg/kg/day. Granuloma was noted in 1 male (#20402) at 50 mg/kg/day and this change was accompanied with calcification. Focal brown pigment deposition of the macrophages was noted in 3 males at 50 mg/kg/day. The macrophages were distributed mainly near the focal necrosis and granuloma. The pigment was stained with Berlin blue, which was hemosiderin.

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Thyroid: Hypertrophy of the follicular cells was noted in 1 male at 0.5 mg/kg/day, 2 males at 5 mg/kg/day, and 3 males and 3 females at 50 mg/kg/day.

Adrenal: Diffuse hypertrophy of the glomerulosa cells was noted in 3 males at 0.5 mg/kg/day, 4 males at 5 mg/kg/day, and all males and 2 females at 50 mg/kg/day. This change was statistically significant in males at 5 and 50 mg/kg/day.

[At the end of the recovery period]

Liver: Centrilobular hypertrophy of hepatocytes was noted in all males and all females at 50 mg/kg/day and this change was statistically significant in males and females at 50 mg/kg/day. However, severity of the hypertrophy decreased in males compared to that at the end of the recovery period. Eosinophilic granular change was noted in cytoplasm of the hypertrophied hepatocytes. Focal necrosis of hepatocytes was noted in 2 males at 50 mg/kg/day. Focal brown pigment deposition of the macrophages was noted in 3 males at 50 mg/kg/day.

Focal proliferation of the bile duct was noted in 4 males at 50 mg/kg/day and this change was statistically significant. This change was not noted at the end of the dosing period.

Thyroid: Hypertrophy of the follicular cells was noted in 3 males and 1 female at 50 mg/kg/day.

Adrenal: Diffuse hypertrophy of the glomerulosa cells was noted in all males and 3 females at 50 mg/kg/day. This change was statistically significant in males at 50 mg/kg/day.

In addition, other changes were noted at the end of the dosing and recovery periods; however, these changes were not considered to be treatment-related because they are spontaneously observed in rats and there was no clear dose-dependency. As for the asymmetry of the testes noted at necropsy, slight diffuse dilatation of the seminiferous tubule was noted histopathologically in the larger side of the testis. As for the nodule of the thyroid noted at necropsy, this change was confirmed histopathologically to be ectopic thymic tissue. These changes are spontaneously observed in rats.

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**8. Discussion and Conclusion**

[CBI] was repeatedly administered by oral gavage at dose levels of 0, 0.5, 5, and 50 mg/kg/day to male and female Cr:CD(SD) rats (SPF) for 28 days to assess the toxicological effects of [CBI] and its reversibility by observing functional and morphological changes.

The body weight decreased in males at 50 mg/kg/day, however, this change recovered by the end of the recovery period.

The food consumption decreased in males at 50 mg/kg/day, however, this change recovered during the dosing period.

In the hematology, the red blood cell count, hemoglobin concentration, and hematocrit decreased in males of all test substance-treated groups and females at 50 mg/kg/day. MCHC decreased in males at 5 and 50 mg/kg/day and females at 50 mg/kg/day. MCH decreased and the platelet count increased in males at 50 mg/kg/day. PT was prolonged in males of all test substance-treated groups and APTT was prolonged in females at 50 mg/kg/day. In these changes, the prolongation of APTT in females did not recover. Decreased red blood cell count, hemoglobin concentration, hematocrit, and MCHC were noted in males at the end of the recovery period, but the reversibility was indicated since these values increased compared to those at the end of the dosing period. In addition, the increased reticulocyte ratio noted in males at the end of the recovery period was considered to be a biological reaction to recover the decreased red blood cell count, hemoglobin concentration, and hematocrit. The other changes in the hematology were not noted at the end of the recovery period and the reversibility was indicated.

In the blood chemistry, the A/G ratio increased in males of all test substance-treated groups and females at 50 mg/kg/day. Albumin increased in males at 5 and 50 mg/kg/day and females at 50 mg/kg/day. Total protein increased in males at 5 mg/kg/day and females at 50 mg/kg/day. Urea nitrogen and glucose increased in males of all test substance-treated groups. ALP and total bilirubin increased in males at 5 and 50 mg/kg/day. Chlorine increased in males at 50 mg/kg/day. In these changes, the increased albumin and total protein recovered in females, but did not recover in males. The increased A/G ratio was noted in males and females at 50 mg/kg/day at the end of the recovery period, but the reversibility was noted since the value decreased compared to that at the end of the dosing period. Other changes in the blood chemistry were not noted at the end of the recovery period and the reversibility was indicated.

In the liver, an increased liver weight, enlargement and brownish change of the liver at

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necropsy, and centrilobular hypertrophy of hepatocytes in the histopathology were noted in males of all test substance-treated groups and females at 50 mg/kg/day. Eosinophilic granular change was noted in cytoplasm of the hypertrophied hepatocytes. The eosinophilic granular change is known to be induced by peroxisome proliferation [1]. In a 14-day repeated dose oral toxicity study in rats [2], enhanced activity of cyanide-insensitive palmitoyl CoA  $\beta$ -oxidation, which is enzyme activity specific to peroxisome in the liver was noted. Therefore, these changes were considered to be related to the peroxisome proliferation. The decreased triglyceride noted in males at 50 mg/kg/day in the blood chemistry test was also considered to be related to the peroxisome proliferation since peroxisome is associated with lipid metabolism. At the end of the recovery period, increased liver weight, enlargement of the liver, and centrilobular hypertrophy of hepatocytes were noted in males and females at 50 mg/kg/day. However, the liver weight in males and females and severity of the centrilobular hypertrophy of hepatocytes in males decreased compared to those at the end of the dosing period and the reversibility was indicated. In the blood chemistry, total cholesterol increased in males at 50 mg/kg/day at the end of the recovery period. It was possible that this change was related to the recovery process of the above-mentioned changes in the liver.

In addition, whitish patch of the liver was noted in males at 5 and 50 mg/kg/day at necropsy at the end of the dosing period. Focal necrosis of hepatocytes was noted histopathologically in males of all test substance-treated groups and females at 50 mg/kg/day. Granuloma and focal brown pigment (hemosiderin) deposition of the macrophages were noted in males at 50 mg/kg/day and were considered to be related to the hepatocyte necrosis. In the blood chemistry, increased ASAT in 1 male at 50 mg/kg/day and increased ALAT in males and females at 50 mg/kg/day were noted and these changes were also considered to be related to the hepatocyte necrosis. At the end of the recovery period, whitish patch of the liver, focal necrosis of hepatocytes, and focal brown pigment deposition of the macrophages were noted in males at 50 mg/kg/day. However, the reversibility was indicated since the incidence of focal necrosis of hepatocytes in males decreased compared to that at the end of the dosing period and this change recovered in females. Focal proliferation of the bile duct was noted in males at 50 mg/kg/day at the end of the recovery period. It was possible that this change was a reactive change to the hepatocyte necrosis since it is known that bile duct proliferation is associated with hepatocyte necrosis [3].

In the thyroid, increased thyroid weight was noted in males at 50 mg/kg/day. Hypertrophy of the follicular cells was noted histopathologically in males of all test substance-treated groups and females at 50 mg/kg/day. It was possible that these

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changes were related to the peroxisome proliferation since hypertrophy of the follicular cells was reported in male rats after the long term dosing of peroxisome proliferator [4]. Hypertrophy of the follicular cells was noted in males and females at 50 mg/kg/day at the end of the recovery period and the reversibility was not observed.

In the adrenal, diffuse hypertrophy of the glomerulosa cells was noted in males of all test substance-treated groups and females at 50 mg/kg/day. It is known that compounds that alter the regulatory rennin-angiotensin system may cause cell enlargement and widening the glomerular zone [5]. However, related changes such as changes in the kidney and serum sodium and potassium levels were not noted in this study. This change was noted in males and females at 50 mg/kg/day at the end of the recovery period and the reversibility was not observed. In addition, increased adrenal weight was noted in males at 50 mg/kg/day at the end of the recovery period.

No treatment-related abnormalities were noted in the clinical observations, detailed clinical observations, function tests, or urinalysis.

Consequently, the no-observed-effect-level (NOEL) of [REDACTED] C B I [REDACTED] was considered to be less than 0.5 mg/kg/day for males and 5 mg/kg/day for females under the conditions of this study. The reversibility of the following changes were not observed after the 2-week recovery period; hypertrophy of the thyroid follicular cells in both sexes, diffuse hypertrophy of the glomerulosa cells of the adrenal in both sexes, increases in serum total protein, albumin, and total cholesterol in males, focal proliferation of the bile duct of the liver in males, increase in adrenal weight in males, and prolongation of APTT in females.

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**9. Reference**

- [1] Cattley RC and Popp JA. 31 Liver. F Hepatocellular Adaptive Responses. 2 Peroxisomes. In: Haschek WM, Rousseaux CG, Wallig MA, editors. Handbook of Toxicologic Pathology, 2nd. San Diego: Academic press; 2002. p.203
- [2] [REDACTED] "A Fourteen-Day Repeated Dose Oral Toxicity Study of [REDACTED] in Rats" [REDACTED]: Final report, [REDACTED] 2009. Study No. B081095
- [3] Greaves P. Liver and Pancreas. Bile ducts, Biliary system. Induced biliary lesions. In: Greaves P, editor. Histopathology of Preclinical Toxicity Studies 3rd. Amsterdam: Elsevier; 2007. p.510-513
- [4] Miller RT, Scappino LA, Long SM, Corton JC. Role of Thyroid Hormones in Hepatic Effects of Peroxisome Proliferators. Toxicol Pathol. 2001. 29(1):149-55
- [5] Greaves P. Endocrine Glands. Adrenal gland. Hypertrophy and diffuse hyperplasia of glomerulosa. In: Greaves P, editor. Histopathology of preclinical toxicity studies 3rd. Amsterdam: Elsevier; 2007. p.809-811

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**10. Study Notes**

**10.1 Unforeseeable circumstances that may have adversely affected the reliability of the study**

None

**10.2 Deviations from the protocol**

None

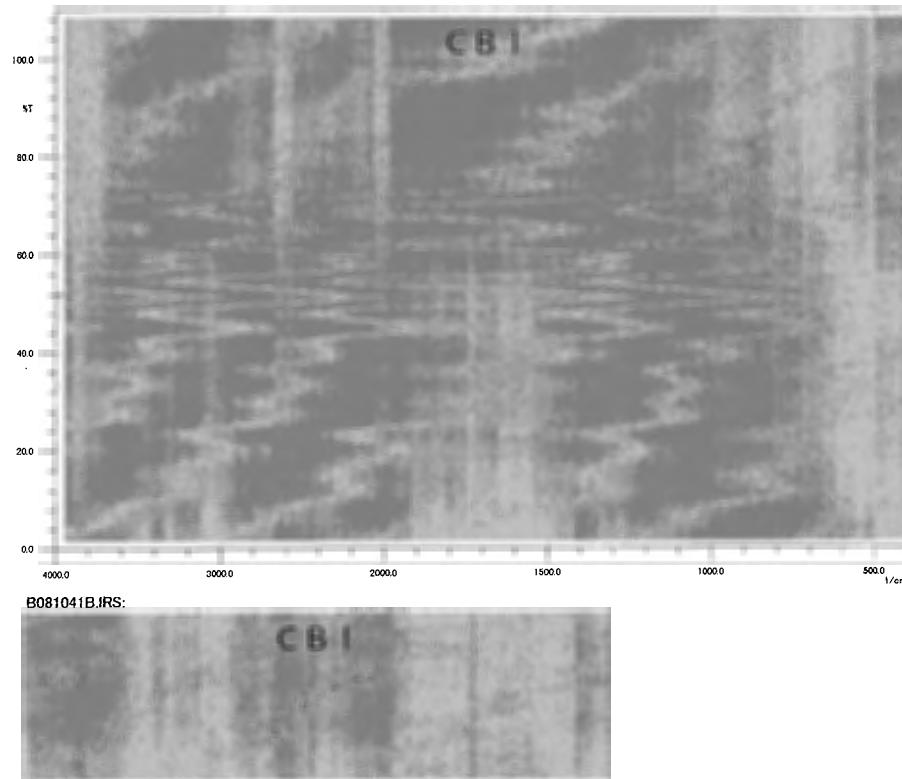
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## 11. Annexes

### 11.1 Infrared absorption spectrum (IR) of the test substance

Before the dosing period

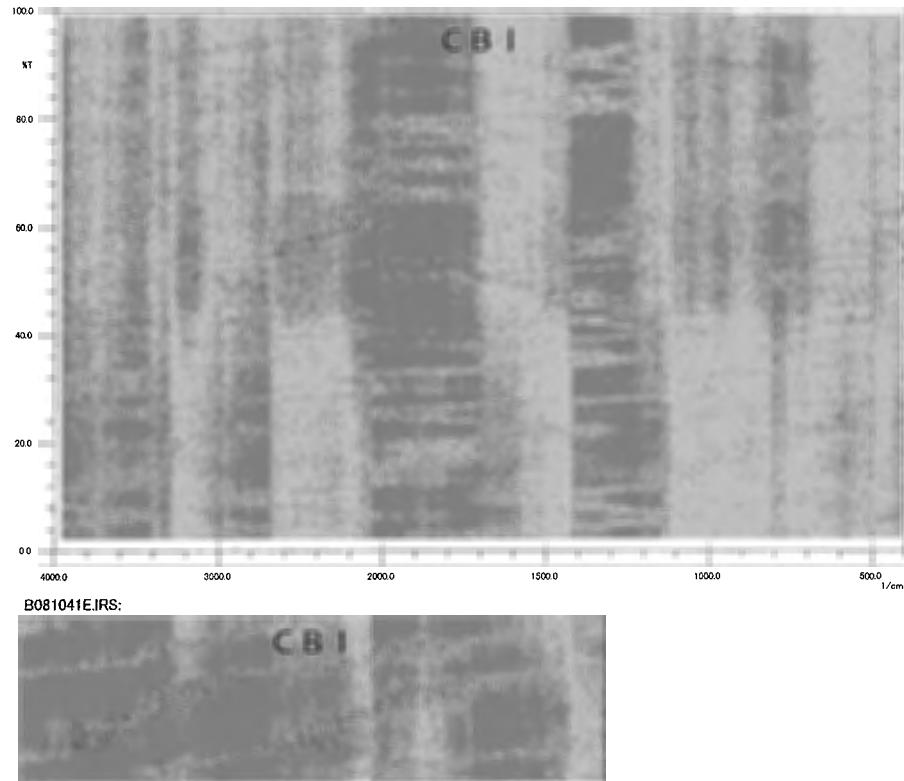


1	407.0	79.082
2	422.4	82.431
3	449.4	88.935
4	461.0	84.458
5	536.2	82.082
6	723.3	75.481
7	819.7	72.116
8	893.0	70.159
9	981.7	55.291
10	1039.6	56.445
11	1091.6	54.541
12	1161.1	29.972
13	1232.4	21.773
14	1305.7	35.213
15	1400.2	45.596
16	1676.0	34.751
17	3120.6	42.791

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After the completion of the dosing period



1	410.8	58.776
2	424.3	56.313
3	445.5	53.029
4	540.0	56.552
5	653.8	54.190
6	682.8	54.859
7	719.4	53.099
8	738.7	49.578
9	771.5	55.943
10	817.8	51.182
11	893.0	50.184
12	981.7	35.952
13	1039.6	38.117
14	1091.6	36.837
15	1161.1	14.451
16	1232.4	9.158
17	1307.6	16.230
18	1400.2	27.973
19	1876.0	20.457
20	2860.2	43.216
21	3126.4	28.812

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## 11.2 Criteria of detailed clinical observations and function tests

### **Detailed clinical observations, hand-held observations**

#### Reactivity on removal from the cage (graded data)

Insert hands into the cage and observe the reactivity of the rats when removing them from the cage.

1. Very easy (nonresistance)
2. Easy (slight escape)
3. Moderately easy (rearing, following observer's hands)
4. Freeze (rigid)
5. Difficult (runs around the cage, hard to grab)
6. Very difficult (attacks observer's hands)

#### Reactivity to handling (graded data)

Observe the reactivity of rats to handling.

1. Very easy (nonresistance)
2. Easy (cautious, lift the limb, slight resistance)
3. Freeze (rigid in observer's hands)
4. Difficult (squirming, body twist, attempting to bite)

#### Aggression

Bite or attempt to bite observer's hands while handling.

- N. None  
P. Present

#### Trauma

Record the position if there is any trauma.

- N. None  
P. Present

#### Color of skin

Observe the change in skin color attributed to peripheral bloodstream (especially pinna).

- N. No abnormality
1. Pale skin
  2. Flush

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Soiled fur

Observe the appearance of the fur with changes attributed to loss of normal grooming.

N. None

P. Present

Exophthalmos

Observe the state of exophthalmos.

N. None

P. Present

Palpebral closure (graded data)

Observe opening of the eyelids.

1. Eyelids wide open
2. Eyelids slightly dropping
3. Eyelids dropping to the halves
4. Closing eyelids

Color of conjunctiva

Observe the change of conjunctiva attributed to peripheral bloodstream.

N. No abnormality

1. Pale

2. Flush

Secretion

Observe secretion around the eyelids.

N. No abnormality

1. Reddish tear (adhesion or discharge of reddish or blackish excreta on the eyelids)
2. Eye discharge (adhesion of eye mucus in or around the eye)

Lacrimation (graded data)

Observe discharge of excessive tear.

N. No abnormality

1. Slight (wet eyes)
2. Moderate (wet around the eyes)
3. Severe (widely wet around the eyes)

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### Salivation (graded data)

Observe discharge of excessive saliva.

- N. No abnormality
- 1. Slight (around the mouth)
- 2. Moderate (up to the chin)
- 3. Severe (greater than moderate)

### Piloerection

Observe the state of bristled fur.

- N. No abnormality
- P. Present (bristled even when stroking the fur)

### Pupil size

Observe the pupil size in light and shade.

- N. No abnormality
- 1. Miosis (constriction of the pupil in the dark)
- 2. Mydriasis (dilatation of the pupil in the light)

## **Detailed clinical observations, open field observations**

### Rearing (discrete value)

Count the number of times the rats rears up on their hind legs without having the front paws touching any surface with and without using wall. However, it does not include rearing for grooming or face washing.

### Arousal (graded data)

Observe the degree of alert and activity without having stimuli in the open field.

- 1. Very low (coma, stupor)
- 2. Low (dull)
- 3. Normal
- 4. High (slightly excited, tense)
- 5. Very high (hyper alert, highly excited)

### Urination

Observe the presence of urination and urine volume.

- N. None
- P. Present (polyuria is recorded)

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### Defecation

Observe the presence of defecation and its condition.

- N. None
- P. Present (diarrhea and loose stool are recorded)

### Posture, body position

N. No abnormality

- 1. Prone position (lying on the stomach sustaining almost the whole body weight ventrally)
- 2. Lateral position (lying on the side)
- 3. Crouching position (lying low, bending extremities, and huddling oneself)
- 4. Hunchback position (leaning forward with the arching back)
- 5. Crawling position (lying on the stomach sustaining almost the whole body weight with elbows)

### Breathing

N. No abnormality

- 1. Irregular respiration (unsteady respiratory rhythm)
- 2. Panting (shallow and rapid respiration while moving only the surface of the body)
- 3. Tachypnea (increasing in depth and rate of respiration)
- 4. Bradypnea (abnormally slow respiration)
- 5. Dyspnea (breathlessness, labored breathing through the mouth at long intervals or rarely breathing)

### Coordination movement

Record if there are any abnormalities.

N. No abnormality

- P. Present (abnormal posture with ankylosed four limbs or staggering gait considered not attributed to exhaustion or loss of muscle strength)

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### Gait

Gently push the rats to walk when they don't walk during the observation.

N. No abnormality

1. Ataxic gait (uncoordinated or irregular)
2. Dragging of hindlimb
3. Shuffling gait (walk showing the bottoms of hindlimb)
4. Tip toe gait (walk on tiptoes)
5. Asthenic gait (hunched body position)
6. Crawling (flattened against surface)
7. Gait disturbance

### Tremor

Observe the tremble of the body with small continual involuntary contraction of the muscle.

N. No abnormality

1. Partial tremor (region is recorded)
2. Tremor of whole body

### Clonic convulsion

Observe the convulsion of four limbs to repeat inflection and extension.

N. No abnormality

1. Partial convulsion (region is recorded)
2. Convulsion of whole body

### Tonic convulsion

N. No abnormality

1. Tonic (constant contraction or extension of hindlimb muscle)
2. Opisthotonus (head and body rigidly arched backward)
3. Emprosthotonus (head and body extended forward)
4. Popcorn convulsion (repeated pops in the air)
5. Asphyxial convulsion (severe convulsions resulting in difficult respiration, depression, or death)

### Stereotypy

Record if there are any abnormalities.

N. No abnormality

- P. Present (e.g. repetitive circling, excessive grooming, pacing, repetitive sniffing, repetitive head movement)

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### Bizarre behavior

Record if there are any abnormalities.

N. No abnormality

P. Present (e.g. self-biting, straub tail, walking backwards, abnormal vocalization, writhing)

### **Function tests, sensory reactivity to stimuli**

#### Approach response (graded data)

Place a blunt stick toward the face for approximately 3 cm and hold for 4 seconds.

1. No reaction
2. Approach slowly to sniff, slightly step backward, or change respiration pattern
3. Freeze
4. Avoid the stick and turn over
5. Jump at stick, attack, or bite

#### Touch response (graded data)

Gently touch the rump with a blunt stick.

1. No reaction
2. Turn slowly toward the touched site, walk forward, or change respiration pattern
3. Freeze
4. Turn immediately toward the touched site or turn to the opposite of the touched site
5. Violent reaction

#### Auditory response (graded data)

Snap fingers directly above the head of rats.

1. No reaction
2. Normal reaction (flinch or flick the ear)
3. Abnormal reaction (jump, move rapidly, or violent reaction)

#### Tail pinch response (graded data)

Gently squeeze the tail about 5 cm from the tip using an extractor.

1. No reaction
2. Turn slowly to look the tail, walk forward
3. Freeze
4. Immediately turn
5. Jump, exaggerated response

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Aerial righting reaction (graded data)

Hold rats in the supine position and drop from 30-cm high to score their landing posture.

1. Land normally with four limbs
2. Slightly uncoordinated
3. Land on side
4. Land on back

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### 11.3 Background data

#### Background data-accumulating conditions

Strain: Crl:CD(SD); Age: 9 weeks old;  
Food: CR-LPF; Period: 2000-2008

Test : Hematology

Study Number	Sex	Item (Unit)	Group	Mean	S.D.	N	Mean -2 S.D.	Mean +2 S.D.	Min.	Max.
B081041	Female	PT (sec)	0 mg/kg	17.08	0.35	5	-	-	-	-
			0.5 mg/kg	17.14	0.71	5	-	-	-	-
			5 mg/kg	17.18	0.47	5	-	-	-	-
			50 mg/kg	15.60	** 0.42	5	-	-	-	-
House Data	Female	PT (sec)	Control	16.5	1.0	124	14.5	18.5	14.4	20.2

Significantly different from control : \*\*,P<0.01.

#### Background data-accumulating conditions

Strain: Crl:CD(SD); Age: 11 weeks old;  
Food: CR-LPF; Period: 2000-2008

Test : Hematology

Study Number	Sex	Item (Unit)	Group	Mean	S.D.	N	Mean -2 S.D.	Mean +2 S.D.	Min.	Max.
B081041	Female	PT (sec)	0 mg/kg	17.08	0.54	5	-	-	-	-
			50 mg/kg	16.26	*	0.05	5	-	-	-
House Data	Female	PT (sec)	Control	16.8	0.8	150	15.2	18.4	14.8	18.7

Significantly different from control : \*,P<0.05.

Test : Blood chcmistry

Study Number	Sex	Item (Unit)	Group	Mean	S.D.	N	Mean -2 S.D.	Mean +2 S.D.	Min.	Max.
B081041	Male	Calcium (mg/dL)	0 mg/kg	10.04	0.18	5	-	-	-	-
			50 mg/kg	10.60	** 0.29	5	-	-	-	-
House Data	Male	Calcium (mg/dL)	Control	10.3	0.3	149	9.7	10.9	9.4	11.0

Significantly different from control : \*\*,P<0.01.

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**Background data-accumulating conditions**

Strain: Crl:CD(SD); Age: 11 weeks old;

Food: CR-LPF; Period: 2000-2008

Test : Blood chemistry

Study Number	Sex	Item (Unit)	Group	Mean	S.D.	N	Mean -2 S.D.	Mean +2 S.D.	Min.	Max.	
B081041	Female	ASAT (U/L)	0 mg/kg	91.0	11.0	5	-	-	-	-	
			50 mg/kg	69.8 *	11.6	5	-	-	-	-	
House Data	Female	ASAT (U/L)	Control	85		17	150	51	119	53	150

Significantly different from control : \*,P<0.05.

Test : Blood chemistry

Study Number	Sex	Item (Unit)	Group	Mean	S.D.	N	Mean -2 S.D.	Mean +2 S.D.	Min.	Max.	
B081041	Female	ALAT (U/L)	0 mg/kg	18.8	0.8	5	-	-	-	-	
			50 mg/kg	14.6 **	1.7	5	-	-	-	-	
House Data	Female	ALAT (U/L)	Control	18		4	150	10	26	13	40

Significantly different from control : \*\*,P<0.01.

Test : Blood chemistry

Study Number	Sex	Item (Unit)	Group	Mean	S.D.	N	Mean -2 S.D.	Mean +2 S.D.	Min.	Max.
B081041	Female	Inorganic Phosphorus (mg/dL)	0 mg/kg	7.20	0.20	5	-	-	-	-
			50 mg/kg	7.58 *	0.19	5	-	-	-	-
House Data	Female	Inorganic Phosphorus (mg/dL)	Control	7.8	0.8	150	6.2	9.4	5.9	9.9

Significantly different from control : \*,P<0.05.

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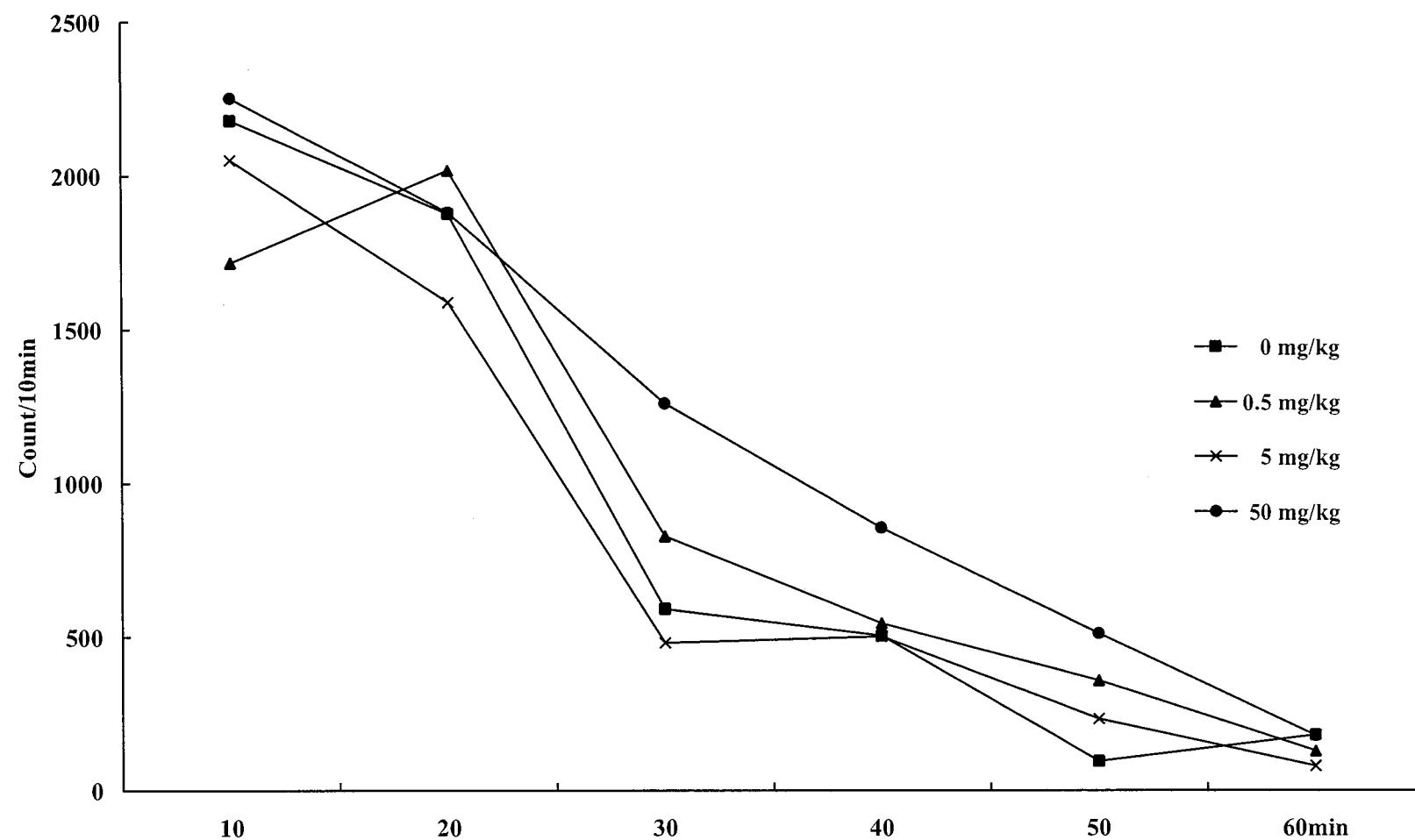


Figure 1-1 Motor Activity (Male, Week 4)

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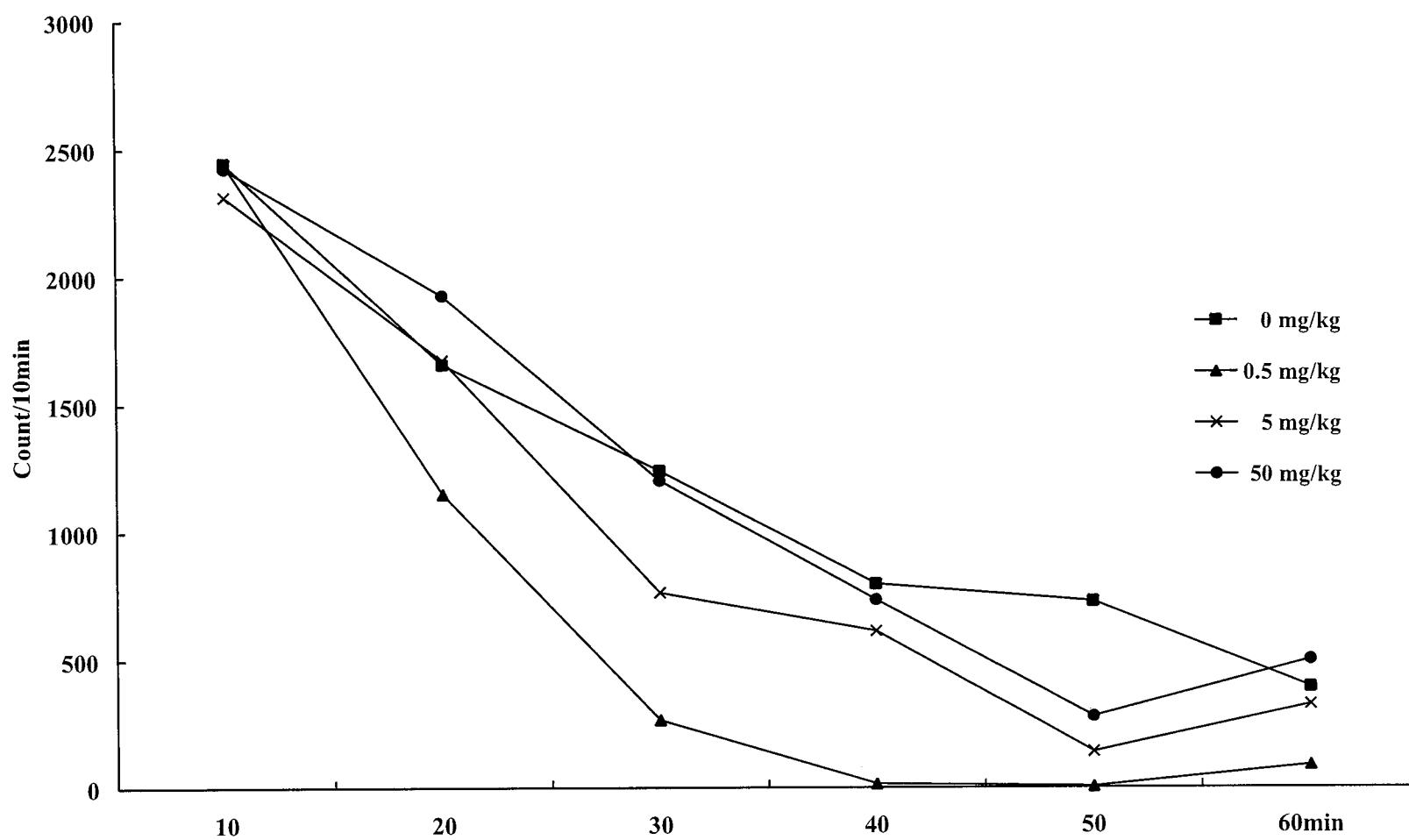
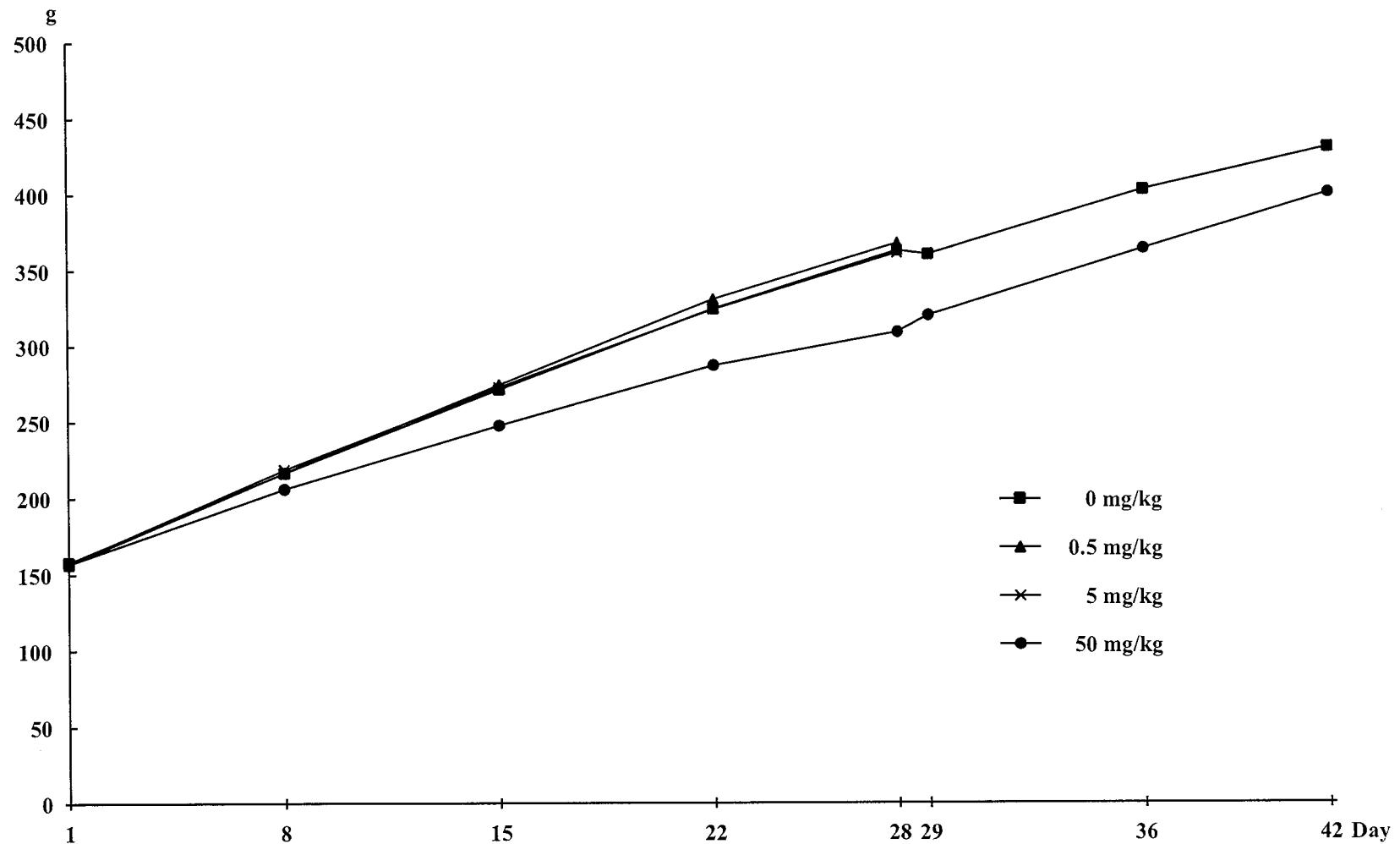


Figure 1-2 Motor Activity (Female, Week 4)

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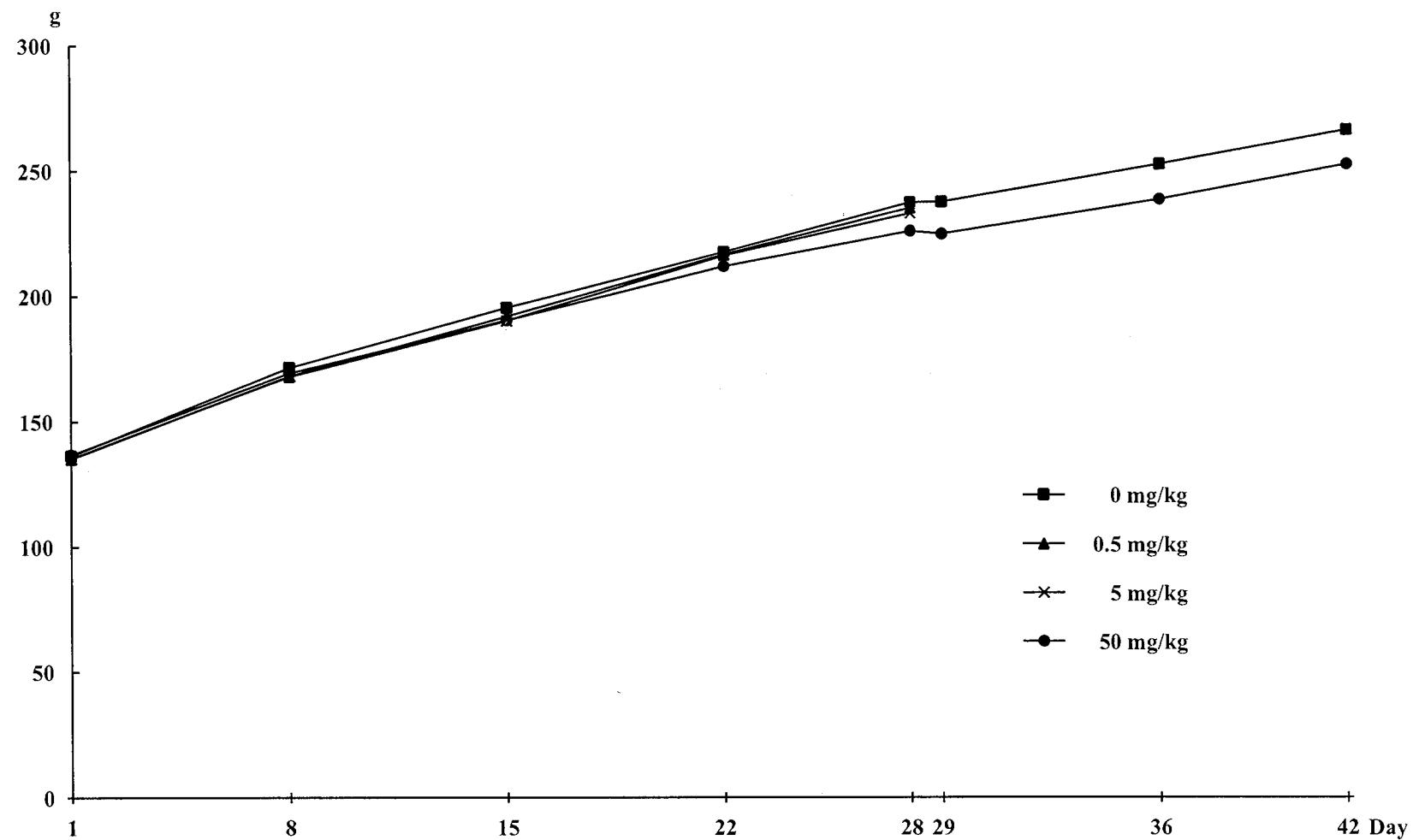
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**Figure 2-1 Body Weight (Male)**

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**Figure 2-2 Body Weight (Female)**

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Table 1 Clinical Sign - Summary

Male

Test Substance Dose	Findings	Day	1	2	3	4	5	6	7	8	9	10	11	12
		Time	10	20	10	20	10	20	10	20	10	20	10	20
<b>CB 1</b> 0 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	10	10	10	10
	No Abnormality		10	10	10	10	10	10	10	10	10	10	10	10
<b>CB 1</b> 0.5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5
<b>CB 1</b> 5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5
<b>CB 1</b> 50 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	10	10	10	10
	No Abnormality		10	10	10	10	10	10	10	10	10	10	10	10
Test Substance Dose	Findings	Day	13	14	15	16	17	18	19	20	21	22	23	24
		Time	10	20	10	20	10	20	10	20	10	20	10	20
<b>CB 1</b> 0 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	10	10	10	10
	No Abnormality		10	10	10	10	10	10	10	10	10	10	10	10
<b>CB 1</b> 0.5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5
<b>CB 1</b> 5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5
<b>CB 1</b> 50 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	10	10	10	10
	No Abnormality		10	10	10	10	10	10	10	10	10	10	10	10

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Table 1 Clinical Sign - Summary

Test Substance Dose	Findings	Day Time	Male																		
			25 10	26 20	27 10	28 20	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
CB 1 0 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5
CB 1 0.5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
CB 1 5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
CB 1 50 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5
	No Abnormality		10	10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Table 1 Clinical Sign - Summary

		Female																									
Test Substance	Findings	Day	Time	1		2		3		4		5		6		7		8		9		10		11			
				10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20		
<b>CB-I</b> 0 mg/kg	Number of Animals	10 10																									
	No Abnormality	10 10																									
<b>CB-I</b> 0.5 mg/kg	Number of Animals	5 5																									
	No Abnormality	5 5																									
<b>CB-I</b> 5 mg/kg	Number of Animals	5 5																									
	No Abnormality	5 5																									
<b>CB-I</b> 50 mg/kg	Number of Animals	10 10																									
	No Abnormality	10 10																									
		Day		13		14		15		16		17		18		19		20		21		22		23		24	
Test Substance	Findings	Time		10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	
				10 10																							
<b>CB-I</b> 0 mg/kg	Number of Animals	10 10																									
	No Abnormality	10 10																									
<b>CB-I</b> 0.5 mg/kg	Number of Animals	5 5																									
	No Abnormality	5 5																									
<b>CB-I</b> 5 mg/kg	Number of Animals	5 5																									
	No Abnormality	5 5																									
<b>CB-I</b> 50 mg/kg	Number of Animals	10 10																									
	No Abnormality	10 10																									

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Table 1 Clinical Sign - Summary

Test Substance Dose	Findings	Day Time	Female																			
			25 10	26 20	27 10	28 20	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	
CB 1 0 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5	5
CB 1 0.5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
CB 1 5 mg/kg	Number of Animals		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
CB 1 50 mg/kg	Number of Animals		10	10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5
	No Abnormality		10	10	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;

Time 10 , Before dosing; Time 20 , After dosing;

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Table 2 Detailed Clinical Observations - Summary

Stage : Week -1

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female					
		C B I					C B I					
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10			
Hand-held observations (Criteria)												
Reactivity on removal from the cage		1	0	0	0	0	0	0	0	0	0	
		2	10	5	5	10	10	5	5	10		
		3	0	0	0	0	0	0	0	0		
		4	0	0	0	0	0	0	0	0		
		5	0	0	0	0	0	0	0	0		
		6	0	0	0	0	0	0	0	0		
Reactivity to handling		1	0	0	0	0	0	0	0	0		
		2	10	5	5	10	10	5	5	10		
		3	0	0	0	0	0	0	0	0		
		4	0	0	0	0	0	0	0	0		
Aggression		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		
Trauma		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		
Color of skin		N	10	5	5	10	10	5	5	10		
		1	0	0	0	0	0	0	0	0		
		2	0	0	0	0	0	0	0	0		
Soiled fur		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		
Exophthalmos		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		

See Annex 11.2 for details of criteria

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Table 2 Detailed Clinical Observations - Summary

Stage : Week -1

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male				Female				
		CB-1		CB-1		CB-1		CB-1		
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	
Hand-held observations		(Criteria)								
Palpebral closure		1	10	5	5	10	10	5	5	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
Color of conjunctiva		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Secretion		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Lacration		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
Salivation		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
Piloerection		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	
Pupil size		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Study No. B081041

Table 2 Detailed Clinical Observations - Summary

Stage : Week -1

Items	Sex Test Substance	Dose Dose Unit	Male				Female				
			0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	
Open field observations		(Criteria)									
Rearing		Mean	8.5	6.6	8.4	6.4	4.9	4.2	5.4	5.0	
		S.D.	2.7	2.5	5.2	3.9	2.8	1.3	1.7	3.7	
Arousal		1	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	
		3	10	5	5	10	10	5	5	10	
		4	0	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	0	
Urination		N	4	2	2	3	8	5	4	7	
		P	6	3	3	7	2	0	1	3	
Defecation		N	6	2	4	6	9	4	4	10	
		P	4	3	1	4	1	1	1	0	
Posture, body position		N	10	5	5	10	10	5	5	10	
		1	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	0	
Breathing		N	10	5	5	10	10	5	5	10	
		1	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Table 2 Detailed Clinical Observations - Summary

Stage : Week -1

Items	Sex Test Substance	Male				Female				
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	
Open field observations		(Criteria)								
Co-ordination movement		N	10	5	5	10	10	5	5	
Gait		P	0	0	0	0	0	0	0	
		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
		6	0	0	0	0	0	0	0	
Tremor		7	0	0	0	0	0	0	0	
		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Clonic convulsion		N	10	5	5	10	10	5	5	
Tonic convulsion		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Stereotypy		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Study No. B081041

Table 2 Detailed Clinical Observations - Summary

Stage : Week -1

Items	Sex	Male				Female			
	Test Substance	0	0.5	5	50	0	0.5	5	50
Dose	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Dose Unit	10	5	5	10	10	5	5	10	10
Number of Animals									
Open field observations	(Criteria)								
Bizarre behaviour	N	10	5	5	10	10	5	5	10
	P	0	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Study No. B081041

Table 3 Detailed Clinical Observations - Summary

Stage : Week 1

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male				Female				
		CB		CB	CB	CB		CB	CB	
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	
Hand-held observations		(Criteria)								
Reactivity on removal from the cage		1	0	0	0	0	0	0	0	
		2	10	5	5	10	10	5	5	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
		6	0	0	0	0	0	0	0	
Reactivity to handling		1	0	0	0	0	0	0	0	
		2	10	5	5	10	10	5	5	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
Aggression		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	
Trauma		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	
Color of skin		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Soiled fur		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	
Exophthalmos		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Table 3 Detailed Clinical Observations - Summary

Stage : Week 1

Items	Sex	Male				Female			
	Test Substance	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg
	Dose	10	5	5	10	10	5	5	10
	Dose Unit								
	Number of Animals								
Hand-held observations	(Criteria)								
Palpebral closure									
	1	10	5	5	10	10	5	5	10
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Color of conjunctiva									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
Secretion									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
Lacration									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
Salivation									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
Piloerection									
	N	10	5	5	10	10	5	5	10
	P	0	0	0	0	0	0	0	0
Pupil size									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Study No. B081041

Table 3 Detailed Clinical Observations - Summary

Stage : Week 1

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male				Female				
		CB		CB		CB		CB		
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	
Open field observations		(Criteria)								
Rearing		Mean	2.4	0.4	1.0	2.9	5.6	6.2	6.0	
		S.D.	1.9	0.5	1.0	2.6	5.4	7.9	3.9	
Arousal		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	10	5	5	10	10	5	10	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
Urination		N	8	1	4	8	7	4	5	
		P	2	4	1	2	3	1	0	
Defecation		N	4	1	3	5	5	3	4	
		P	6	4	2	5	5	2	1	
Posture, body position		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
Breathing		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Table 3 Detailed Clinical Observations - Summary

Stage : Week 1

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female											
		CB		5	10	50	CB		5	10	50							
		0	0.5				mg/kg	mg/kg										
Open field observations		(Criteria)																
Co-ordination movement																		
Gait	N	10	5	5	10	10	5	5	5	10								
	P	0	0	0	0	0	0	0	0	0								
	N	10	5	5	10	10	5	5	5	10								
	1	0	0	0	0	0	0	0	0	0								
	2	0	0	0	0	0	0	0	0	0								
	3	0	0	0	0	0	0	0	0	0								
	4	0	0	0	0	0	0	0	0	0								
	5	0	0	0	0	0	0	0	0	0								
Tremor	6	0	0	0	0	0	0	0	0	0								
	7	0	0	0	0	0	0	0	0	0								
	N	10	5	5	10	10	5	5	5	10								
	1	0	0	0	0	0	0	0	0	0								
	2	0	0	0	0	0	0	0	0	0								
Clonic convulsion	N	10	5	5	10	10	5	5	5	10								
	1	0	0	0	0	0	0	0	0	0								
	2	0	0	0	0	0	0	0	0	0								
	N	10	5	5	10	10	5	5	5	10								
	1	0	0	0	0	0	0	0	0	0								
	2	0	0	0	0	0	0	0	0	0								
Tonic convulsion	N	10	5	5	10	10	5	5	5	10								
	1	0	0	0	0	0	0	0	0	0								
	2	0	0	0	0	0	0	0	0	0								
	3	0	0	0	0	0	0	0	0	0								
	4	0	0	0	0	0	0	0	0	0								
	5	0	0	0	0	0	0	0	0	0								
	N	10	5	5	10	10	5	5	5	10								
	P	0	0	0	0	0	0	0	0	0								
Stereotypy																		

See Annex 11.2 for details of criteria

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Table 3 Detailed Clinical Observations - Summary

Stage : Week 1

Items	Sex	Male				Female			
	Test Substance	0	0.5	5	50	0	0.5	5	50
Dose	mg/kg					mg/kg			
Dose Unit	10	5	5	10		10	5	5	10
Number of Animals									
Open field observations	(Criteria)								
Bizarre behaviour	N	10	5	5	10	10	5	5	10
	P	0	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Study No. B081041

Table 4 Detailed Clinical Observations - Summary

Stage : Week 2

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female												
		CB 1		5	10	5	10	5	10	5	10								
		0	0.5																
<b>Hand-held observations</b>										<b>(Criteria)</b>									
Reactivity on removal from the cage																			
1	0	0	0	0	0	0	0	0	0										
2	10	5	5	10	10	10	5	5	10										
3	0	0	0	0	0	0	0	0	0										
4	0	0	0	0	0	0	0	0	0										
5	0	0	0	0	0	0	0	0	0										
6	0	0	0	0	0	0	0	0	0										
Reactivity to handling																			
1	0	0	0	0	0	0	0	0	0										
2	10	5	5	10	10	10	5	5	10										
3	0	0	0	0	0	0	0	0	0										
4	0	0	0	0	0	0	0	0	0										
Aggression																			
N	10	5	5	10	10	10	5	5	10										
P	0	0	0	0	0	0	0	0	0										
Trauma																			
N	10	5	5	10	10	10	5	5	10										
P	0	0	0	0	0	0	0	0	0										
Color of skin																			
N	10	5	5	10	10	10	5	5	10										
1	0	0	0	0	0	0	0	0	0										
2	0	0	0	0	0	0	0	0	0										
Soiled fur																			
N	10	5	5	10	10	10	5	5	10										
P	0	0	0	0	0	0	0	0	0										
Exophthalmos																			
N	10	5	5	10	10	10	5	5	10										
P	0	0	0	0	0	0	0	0	0										

See Annex 11.2 for details of criteria

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Table 4 Detailed Clinical Observations - Summary

Stage : Week 2

Items	Sex Test Substance	Male				Female			
		C B I		C B I		C B I		C B I	
		0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg
Dose	Number of Animals	10	5	5	10	10	5	5	10
Dose Unit									
Hand-held observations		(Criteria)							
Palpebral closure		1	10	5	5	10	10	5	5
		2	0	0	0	0	0	0	0
		3	0	0	0	0	0	0	0
		4	0	0	0	0	0	0	0
Color of conjunctiva		N	10	5	5	10	10	5	5
		1	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0
Secretion		N	10	5	5	10	10	5	5
		1	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0
Lacration		N	10	5	5	10	10	5	5
		1	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0
		3	0	0	0	0	0	0	0
Salivation		N	10	5	5	10	10	5	5
		1	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0
		3	0	0	0	0	0	0	0
Piloerection		N	10	5	5	10	10	5	5
		P	0	0	0	0	0	0	0
Pupil size		N	10	5	5	10	10	5	5
		1	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Study No. B081041

Table 4 Detailed Clinical Observations - Summary

Stage : Week 2

Items	Sex Test Substance	Male				Female				
		0 mg/kg 10	0.5 mg/kg 5	C B I 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	C B I 5	50 mg/kg 10	
Open field observations		(Criteria)								
Rearing		Mean	1.9	1.4	0.4	0.9	5.4	5.0	4.2	
		S.D.	2.8	2.6	0.5	2.5	4.1	3.9	2.7	
Arousal		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	10	5	5	10	10	5	10	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
Urination		N	7	3	3	4	8	4	2	
		P	3	2	2	6	2	1	3	
Defecation		N	4	4	2	4	8	3	4	
		P	6	1	3	6	2	2	1	
Posture, body position		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
Breathing		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Table 4 Detailed Clinical Observations - Summary

Stage : Week 2

Items	Sex	Male				Female			
	Test Substance	0	0.5	5	50	0	0.5	5	50
	Dose	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Items	Dose Unit	10	5	5	10	10	5	5	10
	Number of Animals								
Open field observations	(Criteria)								
Co-ordination movement	N	10	5	5	10	10	5	5	10
	P	0	0	0	0	0	0	0	0
Gait	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0
	7	0	0	0	0	0	0	0	0
Tremor	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
Clonic convulsion	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
Tonic convulsion	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0
Stereotypy	N	10	5	5	10	10	5	5	10
	P	0	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Table 4 Detailed Clinical Observations - Summary

Stage : Week 2

Items	Sex	Male				Female			
		Test Substance	0	0.5	5	50	0	0.5	5
Dose	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Dose Unit	10	5	5	10	10	5	5	5	10
Number of Animals	(Criteria)								
Open field observations		N	10	5	5	10	10	5	5
Bizarre behaviour		P	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Table 5 Detailed Clinical Observations - Summary

Stage : Week 3

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female					
		CB					CB					
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10			
Hand-held observations		(Criteria)										
Reactivity on removal from the cage		1	0	0	0	0	0	0	0	0	0	
		2	10	5	5	10	10	5	5	10		
		3	0	0	0	0	0	0	0	0		
		4	0	0	0	0	0	0	0	0		
		5	0	0	0	0	0	0	0	0		
		6	0	0	0	0	0	0	0	0		
Reactivity to handling		1	0	0	0	0	0	0	0	0		
		2	10	5	5	10	10	5	5	10		
		3	0	0	0	0	0	0	0	0		
		4	0	0	0	0	0	0	0	0		
Aggression		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		
Trauma		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		
Color of skin		N	10	5	5	10	10	5	5	10		
		1	0	0	0	0	0	0	0	0		
		2	0	0	0	0	0	0	0	0		
Soiled fur		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		
Exophthalmos		N	10	5	5	10	10	5	5	10		
		P	0	0	0	0	0	0	0	0		

See Annex 11.2 for details of criteria

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Table 5 Detailed Clinical Observations - Summary

Stage : Week 3

Items	Sex Test Substance	Male				Female			
		GB		5	50	CB		5	50
		0	0.5			mg/kg	mg/kg		
Items	Dose Dose Unit	10	5	5	10	10	5	5	10
Items	Number of Animals								
Hand-held observations	(Criteria)								
Palpebral closure									
	1	10	5	5	10	10	5	5	10
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Color of conjunctiva									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
Secretion									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
Lacration									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
Salivation									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
Piloerection									
	N	10	5	5	10	10	5	5	10
	P	0	0	0	0	0	0	0	0
Pupil size									
	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Table 5 Detailed Clinical Observations - Summary

Stage : Week 3

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male				Female				
		CB I		CB II		CB I		CB II		
		0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	
Open field observations		(Criteria)								
Rearing		Mean	2.0	2.2	2.2	2.3	3.8	4.0	3.2	
		S.D.	2.8	2.2	1.3	3.1	2.7	4.3	2.3	
Arousal		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	10	5	5	10	10	5	10	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
Urination		N	7	4	4	6	10	0	3	
		P	3	1	1	4	0	5	2	
Defecation		N	6	2	2	5	8	4	4	
		P	4	3	3	5	2	1	0	
Posture, body position		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
Breathing		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Table 5 Detailed Clinical Observations - Summary

Stage : Week 3

Items	Sex Test Substance	Male				Female				
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	
<b>Open field observations</b>		<b>(Criteria)</b>								
Co-ordination movement		N	10	5	5	10	10	5	5	
Gait		P	0	0	0	0	0	0	0	
		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
		5	0	0	0	0	0	0	0	
		6	0	0	0	0	0	0	0	
Tremor		7	0	0	0	0	0	0	0	
		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Clonic convulsion		N	10	5	5	10	10	5	5	
Tonic convulsion		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Stereotypy		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Table 5 Detailed Clinical Observations - Summary

Stage : Week 3

Items	Sex	Male				Female			
	Test Substance	0	0.5	5	50	0	0.5	5	50
Dose	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Dose Unit	10	5	5	10	10	5	5	10	10
Number of Animals									
Open field observations	(Criteria)								
Bizarre behaviour	N	10	5	5	10	10	5	5	10
	P	0	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Table 6 Detailed Clinical Observations - Summary

Stage : Week 4

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female										
		CB		5 mg/kg	10 mg/kg	5 mg/kg	10 mg/kg	CB		5 mg/kg	10 mg/kg						
		0	0.5					0	0.5								
<b>Hand-held observations</b>										<b>(Criteria)</b>							
Reactivity on removal from the cage																	
1	0	0	0	0	0	0	0	0	0								
2	10	5	5	10	10	10	5	5	5								
3	0	0	0	0	0	0	0	0	0								
4	0	0	0	0	0	0	0	0	0								
5	0	0	0	0	0	0	0	0	0								
6	0	0	0	0	0	0	0	0	0								
Reactivity to handling																	
1	0	0	0	0	0	0	0	0	0								
2	10	5	5	10	10	10	5	5	5								
3	0	0	0	0	0	0	0	0	0								
4	0	0	0	0	0	0	0	0	0								
Aggression																	
N	10	5	5	10	10	10	5	5	5								
P	0	0	0	0	0	0	0	0	0								
Trauma																	
N	10	5	5	10	10	10	5	5	5								
P	0	0	0	0	0	0	0	0	0								
Color of skin																	
N	10	5	5	10	10	10	5	5	5								
1	0	0	0	0	0	0	0	0	0								
2	0	0	0	0	0	0	0	0	0								
Soiled fur																	
N	10	5	5	10	10	10	5	5	5								
P	0	0	0	0	0	0	0	0	0								
Exophthalmos																	
N	10	5	5	10	10	10	5	5	5								
P	0	0	0	0	0	0	0	0	0								

See Annex 11.2 for details of criteria

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Table 6 Detailed Clinical Observations - Summary

Stage : Week 4

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male				Female				
		CB		CB	CB	CB		CB	CB	
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	
Hand-held observations		(Criteria)								
Palpebral closure		1	10	5	5	10	10	5	5	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
		4	0	0	0	0	0	0	0	
Color of conjunctiva		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Secretion		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
Lacration		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
Salivation		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	
		3	0	0	0	0	0	0	0	
Piloerection		N	10	5	5	10	10	5	5	
		P	0	0	0	0	0	0	0	
Pupil size		N	10	5	5	10	10	5	5	
		1	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	

See Annex 11.2 for details of criteria

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Table 6 Detailed Clinical Observations - Summary

Stage : Week 4

Items	Sex Test Substance	Male				Female			
		0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10
Open field observations	(Criteria)								
Rearing	Mean	2.6	2.0	4.2	4.6	6.7	6.0	6.8	4.0
	S.D.	3.3	2.3	4.2	3.8	4.1	5.7	2.7	2.9
Arousal	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	10	5	5	10	10	5	5	10
	4	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0
Urination	N	7	5	4	8	8	3	2	7
	P	3	0	1	2	2	2	3	3
Defecation	N	5	2	2	7	9	3	4	9
	P	5	3	3	3	1	2	1	1
Posture, body position	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0
Breathing	N	10	5	5	10	10	5	5	10
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Table 6 Detailed Clinical Observations - Summary

Stage : Week 4

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female					
		CB I		CB II		CB III		CB I		CB II		
		0 mg/kg	0.5 mg/kg	5 mg/kg	10 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	10 mg/kg	0 mg/kg	0.5 mg/kg	
Open field observations		(Criteria)										
Co-ordination movement												
Gait	N	10	5	5	10	10	5	5	10			
	P	0	0	0	0	0	0	0	0			
	N	10	5	5	10	10	5	5	10			
	1	0	0	0	0	0	0	0	0			
	2	0	0	0	0	0	0	0	0			
	3	0	0	0	0	0	0	0	0			
	4	0	0	0	0	0	0	0	0			
	5	0	0	0	0	0	0	0	0			
Tremor	N	10	5	5	10	10	5	5	10			
	1	0	0	0	0	0	0	0	0			
	2	0	0	0	0	0	0	0	0			
	N	10	5	5	10	10	5	5	10			
	1	0	0	0	0	0	0	0	0			
	2	0	0	0	0	0	0	0	0			
Clonic convulsion	N	10	5	5	10	10	5	5	10			
	1	0	0	0	0	0	0	0	0			
	2	0	0	0	0	0	0	0	0			
	N	10	5	5	10	10	5	5	10			
	1	0	0	0	0	0	0	0	0			
	2	0	0	0	0	0	0	0	0			
Tonic convulsion	N	10	5	5	10	10	5	5	10			
	1	0	0	0	0	0	0	0	0			
	2	0	0	0	0	0	0	0	0			
	3	0	0	0	0	0	0	0	0			
	4	0	0	0	0	0	0	0	0			
	5	0	0	0	0	0	0	0	0			
	N	10	5	5	10	10	5	5	10			
	P	0	0	0	0	0	0	0	0			
Stereotypy												

See Annex 11.2 for details of criteria

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Table 6 Detailed Clinical Observations - Summary

Stage : Week 4

Items	Sex	Test Substance	Male				Female			
			0	0.5	5	50	0	0.5	5	50
Dose	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Dose Unit	10	5	5	10	10	5	5	5	10	10
Number of Animals										
Open field observations	(Criteria)									
Bizarre behaviour			N	10	5	5	10	10	5	5
			P	0	0	0	0	0	0	0

See Annex 11.2 for details of criteria

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Table 7 Function Tests - Summary

Stage : Week 4

Items	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female										
		C B I		5 mg/kg	10 mg/kg	5 mg/kg	10 mg/kg	C B I		5 mg/kg	10 mg/kg						
		0 mg/kg	0.5 mg/kg					0 mg/kg	0.5 mg/kg								
<b>Sensory reactivity to stimuli</b>										<b>(Criteria)</b>							
Approach response																	
Touch response	1	0	0	0	0	0	0	0	0	0	0						
	2	10	5	5	10	10	5	5	5	10							
	3	0	0	0	0	0	0	0	0	0	0						
	4	0	0	0	0	0	0	0	0	0	0						
	5	0	0	0	0	0	0	0	0	0	0						
Auditory response																	
Tail pinch response	1	0	0	0	0	0	0	0	0	0	0						
	2	10	5	5	10	10	5	5	5	10							
	3	0	0	0	0	0	0	0	0	0	0						
Aerial righting reaction																	
	1	10	5	5	10	10	5	5	5	10							
	2	0	0	0	0	0	0	0	0	0							
	3	0	0	0	0	0	0	0	0	0							
	4	0	0	0	0	0	0	0	0	0							

See Annex 11.2 for details of criteria

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Table 7 Function Tests - Summary

Stage : Week 4

Items	Sex	Test Substance	Male				Female			
			0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10	0 mg/kg 10	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 10
Grip strength										
Forelimb (g)										
	Mean	841.2	947.0	865.4	791.4	755.2	773.2	729.8	764.0	
	S.D.	122.8	115.8	105.5	97.2	133.5	70.5	89.6	90.3	
Hindlimb (g)										
	Mean	609.6	639.2	626.2	558.7	558.6	555.4	514.0	506.0	
	S.D.	94.5	74.5	128.2	119.0	61.3	65.3	84.3	83.4	

See Annex 11.2 for details of criteria

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Table 8 Motor Activity - Summary      Stage : Week 4      Male

Test Substance Dose	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
[REDACTED] 0 mg/kg	Mean	2180.6	1876.5	590.8	503.4	94.9	180.4	5426.6
	S.D.	407.1	551.3	647.1	1005.3	166.1	318.8	2105.4
	n	10	10	10	10	10	10	10
[REDACTED] 0.5 mg/kg	Mean	1716.4	2016.4	828.4	544.8	357.8	129.4	5593.2
	S.D.	1007.8	344.4	779.9	647.0	688.1	150.1	1653.2
	n	5	5	5	5	5	5	5
[REDACTED] 5 mg/kg	Mean	2050.6	1588.4	481.6	501.4	233.0	80.0	4935.0
	S.D.	319.4	203.2	620.5	1119.5	429.6	100.8	2224.3
	n	5	5	5	5	5	5	5
[REDACTED] 50 mg/kg	Mean	2252.1	1880.4	1259.2	854.6	511.0	178.5	6935.8
	S.D.	182.4	203.6	605.6	829.5	724.7	389.9	2312.7
	n	10	10	10	10	10	10	10

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Table 8 Motor Activity - Summary      Stage : Week 4      Female

Test Substance Dose	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
CB I 0 mg/kg	Mean	2445.0	1657.1	1241.1	798.0	729.2	394.0	7264.4
	S.D.	288.7	712.1	838.7	900.3	823.1	577.6	2973.9
	n	10	10	10	10	10	10	10
CB I 0.5 mg/kg	Mean	2441.8	1151.0	265.6	14.6	3.6 **	87.8	3964.4
	S.D.	248.7	919.3	294.7	15.8	7.0	94.3	1179.4
	n	5	5	5	5	5	5	5
CB I 5 mg/kg	Mean	2314.0	1674.4	765.2	613.8	140.4	324.6	5832.4
	S.D.	277.4	665.3	1011.1	904.8	202.6	466.4	2610.3
	n	5	5	5	5	5	5	5
CB I 50 mg/kg	Mean	2424.7	1927.0	1203.1	736.5	279.2	500.2	7070.7
	S.D.	343.7	556.9	882.0	804.7	554.9	821.2	3083.4
	n	10	10	10	10	10	10	10

Significantly different from control : \*\*,P<0.01.

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Table 9 Body Weight - Summary

Test Substance Dose	Day	Male								Unit : g
		1	8	15	22	28	29	36	42	
C B I	Mean	157.9	216.3	271.1	324.1	362.5	360.0	402.4	430.0	
0 mg/kg	S.D.	4.1	8.7	13.2	17.4	21.8	18.9	18.4	19.3	
	n	10	10	10	10	10	5	5	5	
C B I	Mean	156.8	216.6	274.2	330.4	367.2				
0.5 mg/kg	S.D.	7.6	11.4	14.5	25.8	30.0				
	n	5	5	5	5	5				
C B I	Mean	157.4	218.4	272.6	323.8	361.0				
5 mg/kg	S.D.	7.1	14.4	21.5	27.8	31.4				
	n	5	5	5	5	5				
C B I	Mean	156.9	205.8	247.5 **	286.9 **	308.6 **	319.6 *	363.6 *	400.2	
50 mg/kg	S.D.	6.2	12.0	17.2	24.1	32.1	26.3	24.6	26.1	
	n	10	10	10	10	10	5	5	5	

Significantly different from control : \*,P<0.05; \*\*,P<0.01.

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Table 9 Body Weight - Summary

Female

Unit : g

Test Substance Dose	Day	1	8	15	22	28	29	36	42
CBI	Mean	136.4	171.5	195.2	217.4	237.2	237.4	252.4	266.0
0 mg/kg	S.D.	6.8	11.1	11.6	14.6	16.1	16.3	18.3	23.3
	n	10	10	10	10	10	5	5	5
CBI	Mean	135.2	168.0	191.8	216.4	235.0			
0.5 mg/kg	S.D.	7.3	12.6	15.6	22.2	27.7			
	n	5	5	5	5	5			
CBI	Mean	135.4	167.8	190.0	216.0	232.8			
5 mg/kg	S.D.	7.1	5.9	14.0	15.6	15.1			
	n	5	5	5	5	5			
CBI	Mean	136.8	169.3	190.2	211.7	225.8	224.6	238.4	252.4
50 mg/kg	S.D.	4.9	8.7	8.1	14.9	11.9	17.9	14.4	24.8
	n	10	10	10	10	10	5	5	5

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Table 10 Food Consumption - Summary

Male

Unit : g/animal/day

Test Substance Dose	Day	8	15	22	26	36	40
CB 1 0 mg/kg	Mean	25.54	28.33	30.80	30.30	31.60	32.22
	S.D.	1.10	2.00	2.31	1.90	1.75	1.49
	n	10	10	10	10	5	5
CB 1 0.5 mg/kg	Mean	25.18	28.10	30.50	30.18		
	S.D.	2.00	2.13	2.36	1.83		
	n	5	5	5	5		
CB 1 5 mg/kg	Mean	25.88	29.66	34.32	34.28		
	S.D.	2.17	2.72	2.86	3.48		
	n	5	5	5	5		
CB 1 50 mg/kg	Mean	23.43 *	29.17	30.87	29.11	32.06	31.06
	S.D.	1.80	3.28	3.40	4.44	3.35	2.66
	n	10	10	10	10	5	5

Significantly different from control : \*,P<0.05.

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Study No. B081041

Table 10 Food Consumption - Summary

Female

Unit : g/animal/day

Test Substance Dose	Day	8	15	22	26	36	40
CB.1 0 mg/kg	Mean	20.19	21.27	22.31	21.85	23.28	23.12
	S.D.	1.52	1.52	1.38	1.53	1.67	1.75
	n	10	10	10	10	5	5
CB.1 0.5 mg/kg	Mean	19.12	20.46	21.88	21.78		
	S.D.	2.14	2.44	3.34	2.85		
	n	5	5	5	5		
CB.1 5 mg/kg	Mean	19.02	20.74	22.36	21.44		
	S.D.	0.78	1.40	1.01	0.82		
	n	5	5	5	5		
CB.1 50 mg/kg	Mean	19.21	19.97	21.19	20.56	22.48	21.72
	S.D.	0.88	0.89	0.94	1.14	1.85	1.53
	n	10	10	10	10	5	5

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Study No. B081041

Table 11 Hematology - Summary

Male

Test Substance	Red Blood Cell Count		Hemoglobin conc.		Hematocrit		MCV		MCH					
	x10 <sup>6</sup> /µL	Day 29	Day 43	g/dL	Day 29	Day 43	%	fL	Day 29	Day 43	pg	Day 29	Day 43	
C.B.I.	Mean	8.208	8.286	16.12	15.98	45.96	44.94	56.04	54.24	19.66	19.28			
0 mg/kg	S.D.	0.320	0.194	0.42	0.75	1.11	1.98	1.69	1.99	0.32	0.77			
	n	5	5	5	5	5	5	5	5	5	5			
C.B.I.	Mean	7.398 *		14.74 *		42.70 *		57.80		19.94				
0.5 mg/kg	S.D.	0.509		0.81		1.95		2.00		0.81				
	n	5		5		5		5		5				
C.B.I.	Mean	7.234 *		14.38 **		42.02 **		58.28		19.92				
5 mg/kg	S.D.	0.611		0.84		1.84		2.56		0.61				
	n	5		5		5		5		5				
C.B.I.	Mean	7.272 *	7.508 *	13.34 **	14.06 **	39.26 **	41.08 **	53.98	54.90	18.34 **	18.78			
50 mg/kg	S.D.	0.329	0.589	0.83	0.71	2.20	1.45	1.25	3.10	0.50	0.88			
	n	5	5	5	5	5	5	5	5	5	5			
Test Substance		MCHC		Platelet Count		Reticulocyte Ratio		PT		APTT				
Dose		g/dL	Day 29	Day 43	x10 <sup>3</sup> /µL	Day 29	Day 43	%	sec	Day 29	Day 43	sec	Day 29	Day 43
C.B.I.	Mean	35.06	35.58	1156.6	1225.2	4.088	4.126	21.98	18.78	21.96	19.84			
0 mg/kg	S.D.	0.57	0.16	112.1	24.3	0.328	0.743	4.20	1.96	2.34	1.60			
	n	5	5	5	5	5	5	5	5	5	5			
C.B.I.	Mean	34.50		1204.2		5.300		24.80		21.92				
0.5 mg/kg	S.D.	0.51		175.1		1.248		7.37		2.05				
	n	5		5		5		5		5				
C.B.I.	Mean	34.20 *		1218.6		5.412		24.40		22.76				
5 mg/kg	S.D.	0.57		68.5		1.029		4.44		1.00				
	n	5		5		5		5		5				
C.B.I.	Mean	33.96 *	34.22 **	1454.8 **	1287.4	4.518	6.432 **	24.16	21.16	22.20	21.78			
50 mg/kg	S.D.	0.42	0.54	133.1	147.6	0.316	1.131	3.86	4.26	2.59	2.40			
	n	5	5	5	5	5	5	5	5	5	5			

Significantly different from control : \*,P<0.05; \*\*,P<0.01.

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Study No. B081041

Table 11 Hematology - Summary

Male

Test Substance	White Blood Cell Count x10 <sup>3</sup> /µL		Lymphocyte		Neutrophil		Eosinophil		Basophil			
	Dose	Day 29	Day 43	%	Day 29	Day 43	%	Day 29	Day 43	%	Day 29	Day 43
CB.I	Mean	10.358	10.652		80.80	79.64		15.60	15.52		0.94	0.96
0 mg/kg	S.D.	2.475	3.256		3.93	4.90		3.84	4.50		0.38	0.40
	n	5	5		5	5		5	5		5	5
CB.I	Mean	11.764			80.90			14.86			0.96	
0.5 mg/kg	S.D.	2.344			4.14			3.38			0.23	
	n	5			5			5			5	
CB.I	Mean	12.690			82.20			14.16			0.80	
5 mg/kg	S.D.	3.527			3.88			3.77			0.17	
	n	5			5			5			5	
CB.I	Mean	13.490	11.816		77.36	79.62		18.54	15.86		1.06	0.92
50 mg/kg	S.D.	3.530	1.219		4.86	2.61		4.87	1.79		0.80	0.43
	n	5	5		5	5		5	5		5	5
<hr/>												
Test Substance												
Monocyte												
<hr/>												
%												
Dose												
CB.I	Mean	2.62	3.84									
0 mg/kg	S.D.	0.26	0.63									
	n	5	5									
CB.I	Mean	3.24										
0.5 mg/kg	S.D.	1.08										
	n	5										
CB.I	Mean	2.76										
5 mg/kg	S.D.	0.99										
	n	5										
CB.I	Mean	2.98	3.60									
50 mg/kg	S.D.	1.01	1.13									
	n	5	5									

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Table 11 Hematology - Summary

Female

Test Substance		Red Blood Cell Count x10 <sup>6</sup> /µL		Hemoglobin conc. g/dL		Hematocrit %		MCV fL		MCH pg	
Dose		Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
CBI	Mean	7.824	8.228	15.68	15.64	44.00	43.56	56.28	52.98	20.06	19.02
	S.D.	0.424	0.413	0.66	0.63	1.55	1.49	1.58	1.25	0.50	0.27
	n	5	5	5	5	5	5	5	5	5	5
CBI	Mean	7.882		15.56		43.46		55.16		19.76	
	S.D.	0.301		0.53		1.26		1.04		0.32	
	n	5		5		5		5		5	
CBI	Mean	7.696		15.26		42.76		55.60		19.82	
	S.D.	0.434		0.72		1.86		1.49		0.29	
	n	5		5		5		5		5	
CBI	Mean	7.208 *	7.828	14.44 *	14.90	41.34	42.22	57.36	53.98	20.02	19.04
	S.D.	0.241	0.193	0.50	0.20	1.58	0.90	1.42	2.33	0.40	0.57
	n	5	5	5	5	5	5	5	5	5	5
Test Substance		MCHC g/dL		Platelet Count x10 <sup>3</sup> /µL		Reticulocyte Ratio %		PT sec		APTT sec	
Dose		Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
CBI	Mean	35.62	35.90	1202.6	1126.8	3.312	3.728	17.08	17.08	15.26	15.90
	S.D.	0.33	0.33	102.1	92.3	0.670	0.892	0.35	0.54	0.74	1.02
	n	5	5	5	5	5	5	5	5	5	5
CBI	Mean	35.80		1082.0		3.310		17.14		15.42	
	S.D.	0.32		72.0		0.339		0.71		0.90	
	n	5		5		5		5		5	
CBI	Mean	35.68		1140.6		3.312		17.18		15.20	
	S.D.	0.54		190.2		0.456		0.47		0.49	
	n	5		5		5		5		5	
CBI	Mean	34.96 *	35.28	1079.4	1062.8	3.018	3.328	15.60 **	16.26 *	18.00 **	17.50 *
	S.D.	0.23	0.51	101.5	124.2	0.480	0.706	0.42	0.05	1.41	0.73
	n	5	5	5	5	5	5	5	5	5	5

Significantly different from control : \*, P<0.05; \*\*, P<0.01.

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Table 11 Hematology - Summary

Female

Test Substance	White Blood Cell Count		Lymphocyte		Neutrophil		Eosinophil		Basophil	
	x10 <sup>3</sup> /µL		%		%		%		%	
Dose	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
CB I	Mean	8.180	8.506	85.38	78.06	11.00	17.48	1.20	1.20	0.02
0 mg/kg	S.D.	1.951	3.051	4.17	4.43	4.60	4.86	0.52	0.42	0.04
	n	5	5	5	5	5	5	5	5	5
CB I	Mean	8.778		84.86		10.80		1.00		0.00
0.5 mg/kg	S.D.	2.042		4.57		3.45		0.34		0.00
	n	5		5		5		5		5
CB I	Mean	9.706		82.40		13.66		1.20		0.06
5 mg/kg	S.D.	2.208		8.19		7.71		0.45		0.05
	n	5		5		5		5		5
CB I	Mean	11.406	6.666	89.22	84.22	7.78	12.10	0.60	0.78	0.02
50 mg/kg	S.D.	4.452	1.544	3.98	7.71	3.42	6.76	0.34	0.22	0.04
	n	5	5	5	5	5	5	5	5	5
<hr/>										
Test Substance										
Monocyte										
<hr/>										
%										
Dose	Day 29		Day 43							
CB I	Mean	2.40		3.24						
0 mg/kg	S.D.	1.03		1.13						
	n	5		5						
CB I	Mean	3.34								
0.5 mg/kg	S.D.	1.37								
	n	5								
CB I	Mean	2.68								
5 mg/kg	S.D.	0.76								
	n	5								
CB I	Mean	2.38		2.88						
50 mg/kg	S.D.	0.36		0.99						
	n	5		5						

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Table 12 Blood Chemistry - Summary

Male

Test Substance	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin mg/dL		
	Dose	U/L Day 29	U/L Day 43	U/L Day 29	U/L Day 43	U/L Day 29	U/L Day 43	U/L Day 29	U/L Day 43	Day 29	Day 43
C.B.I.	Mean	87.6	103.4	21.8	26.2	1.0	1.0	672.2	538.6	0.00	0.04
0 mg/kg	S.D.	14.3	17.3	4.0	2.3	0.0	0.0	77.3	70.5	0.00	0.05
	n	5	5	5	5	5	5	5	5	5	5
C.B.I.	Mean	88.4		26.4		0.8		885.8		0.02	
0.5 mg/kg	S.D.	10.1		4.6		0.4		231.4		0.04	
	n	5		5		5		5		5	
C.B.I.	Mean	96.6		30.0		0.8		1078.8 **		0.08 *	
5 mg/kg	S.D.	7.0		5.6		0.4		253.9		0.04	
	n	5		5		5		5		5	
C.B.I.	Mean	119.2	88.2	45.6 **	37.0	0.8	0.4	1205.0 **	545.2	0.10 **	0.00
50 mg/kg	S.D.	43.9	18.4	26.6	9.5	0.4	0.5	123.5	81.2	0.00	0.00
	n	5	5	5	5	5	5	5	5	5	5
Test Substance	Urea Nitrogen mg/dL		Creatinine mg/dL		Glucose mg/dL		Total Cholesterol mg/dL		Triglyceride mg/dL		
	Dose	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
C.B.I.	Mean	12.12	12.52	0.20	0.22	128.2	119.4	68.4	69.6	33.6	32.4
0 mg/kg	S.D.	1.84	2.37	0.00	0.04	5.9	6.3	15.6	8.6	7.5	12.6
	n	5	5	5	5	5	5	5	5	5	5
C.B.I.	Mean	16.46 *		0.20		146.6 *		53.4		29.4	
0.5 mg/kg	S.D.	3.05		0.00		9.9		19.5		6.1	
	n	5		5		5		5		5	
C.B.I.	Mean	16.52 *		0.18		147.2 *		54.4		25.2	
5 mg/kg	S.D.	1.86		0.04		13.2		16.6		3.6	
	n	5		5		5		5		5	
C.B.I.	Mean	17.92 **	10.88	0.18	0.20	151.6 **	129.8	78.8	123.2 **	22.2 *	32.2
50 mg/kg	S.D.	1.49	1.31	0.04	0.00	6.5	16.9	32.3	20.3	6.3	10.5
	n	5	5	5	5	5	5	5	5	5	5

Significantly different from control : \*, P<0.05; \*\*, P<0.01.

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Study No. B081041

Table 12 Blood Chemistry - Summary

Male

Test Substance	Total Protein g/dL		Albumin g/dL		A/G Ratio		Calcium mg/dL		Inorganic Phosphorus mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
Dose										
CB 1	Mean	6.46	6.56	3.10	3.06	0.940	0.868	10.26	10.04	9.12
0 mg/kg	S.D.	0.19	0.09	0.07	0.05	0.094	0.036	0.24	0.18	0.44
	n	5	5	5	5	5	5	5	5	5
CB 1	Mean	6.36		3.48		1.198 **		9.94		9.74
0.5 mg/kg	S.D.	0.25		0.11		0.080		0.21		0.66
	n	5		5		5		5		5
CB 1	Mean	6.92 *		3.82 **		1.242 **		10.32		10.00
5 mg/kg	S.D.	0.15		0.08		0.064		0.08		0.65
	n	5		5		5		5		5
CB 1	Mean	6.52	7.36 **	3.72 *	3.68 **	1.314 **	1.002 **	10.04	10.60 **	9.40
50 mg/kg	S.D.	0.26	0.29	0.29	0.15	0.139	0.063	0.38	0.29	0.43
	n	5	5	5	5	5	5	5	5	5
Test Substance	Na mmol/L		K mmol/L		Cl mmol/L					
Dose	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43				
CB 1	Mean	147.0	146.2	4.28	4.46	103.2				
0 mg/kg	S.D.	0.7	1.5	0.29	0.21	0.8				
	n	5	5	5	5	5				
CB 1	Mean	146.8		4.38		104.8				
0.5 mg/kg	S.D.	1.1		0.08		1.1				
	n	5		5		5				
CB 1	Mean	145.4		4.66		103.0				
5 mg/kg	S.D.	1.8		0.32		1.4				
	n	5		5		5				
CB 1	Mean	146.0	145.0	4.48	4.44	105.2 *				
50 mg/kg	S.D.	0.7	0.7	0.29	0.19	1.3				
	n	5	5	5	5	5				

Significantly different from control : \*,P<0.05; \*\*,P<0.01.

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Study No. B081041

Table 12 Blood Chemistry - Summary

Female

Test Substance	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin mg/dL		
	Dose	U/L Day 29	U/L Day 43	U/L Day 29	U/L Day 43	U/L Day 29	U/L Day 43	U/L Day 29	U/L Day 43	Day 29	Day 43
C B I	Mean	86.4	91.0	16.2	18.8	1.0	0.8	323.4	235.2	0.02	0.04
0 mg/kg	S.D.	6.4	11.0	2.3	0.8	0.0	0.4	80.7	57.7	0.04	0.05
	n	5	5	5	5	5	5	5	5	5	5
C B I	Mean	82.4		16.6		1.0		336.0		0.00	
0.5 mg/kg	S.D.	9.4		1.1		0.0		25.2		0.00	
	n	5		5		5		5		5	
C B I	Mean	98.4		17.2		0.8		252.4		0.00	
5 mg/kg	S.D.	19.8		2.9		0.4		29.9		0.00	
	n	5		5		5		5		5	
C B I	Mean	99.6	69.8 *	21.4 *	14.6 **	0.8	0.6	249.6	182.0	0.00	0.00
50 mg/kg	S.D.	27.6	11.6	4.0	1.7	0.4	0.5	57.8	68.1	0.00	0.00
	n	5	5	5	5	5	5	5	5	5	5
Test Substance	Urea Nitrogen mg/dL		Creatinine mg/dL		Glucose mg/dL		Total Cholesterol mg/dL		Triglyceride mg/dL		
	Dose	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
C B I	Mean	11.70	13.98	0.20	0.24	117.0	118.2	88.4	90.6	12.2	16.2
0 mg/kg	S.D.	2.40	2.33	0.00	0.05	7.1	14.8	13.3	11.1	4.3	6.4
	n	5	5	5	5	5	5	5	5	5	5
C B I	Mean	11.70		0.22		107.8		77.8		18.4	
0.5 mg/kg	S.D.	0.57		0.04		17.2		17.2		11.7	
	n	5		5		5		5		5	
C B I	Mean	12.62		0.22		109.2		76.0		15.6	
5 mg/kg	S.D.	2.22		0.04		10.4		9.1		4.5	
	n	5		5		5		5		5	
C B I	Mean	13.30	13.56	0.20	0.22	118.6	124.0	86.8	80.6	19.4	22.4
50 mg/kg	S.D.	2.24	2.38	0.00	0.04	5.4	3.7	10.5	10.1	1.8	5.0
	n	5	5	5	5	5	5	5	5	5	5

Significantly different from control : \*, P<0.05; \*\*, P<0.01.

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Study No. B081041

Table 12 Blood Chemistry - Summary

Female

Test Substance		Total Protein g/dL		Albumin g/dL		A/G Ratio		Calcium mg/dL		Inorganic Phosphorus mg/dL	
Dose		Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
<b>C B I</b> 0 mg/kg	Mean	6.48	6.88	3.22	3.34	0.978	0.944	10.30	10.16	8.34	7.20
	S.D.	0.28	0.40	0.23	0.32	0.061	0.091	0.20	0.81	0.43	0.20
	n	5	5	5	5	5	5	5	5	5	5
<b>C B I</b> 0.5 mg/kg	Mean	6.44		3.20		0.986		10.32		8.40	
	S.D.	0.23		0.16		0.055		0.48		0.58	
	n	5		5		5		5		5	
<b>C B I</b> 5 mg/kg	Mean	6.68		3.40		1.044		10.32		8.34	
	S.D.	0.31		0.12		0.052		0.18		0.25	
	n	5		5		5		5		5	
<b>C B I</b> 50 mg/kg	Mean	7.52 **	7.14	4.06 **	3.68	1.162 **	1.064 *	10.66	10.46	8.22	7.58 *
	S.D.	0.19	0.26	0.15	0.15	0.066	0.056	0.25	0.29	0.49	0.19
	n	5	5	5	5	5	5	5	5	5	5

Test Substance		Na mmol/L		K mmol/L		Cl mmol/L	
Dose		Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
<b>C B I</b> 0 mg/kg	Mean	145.0	145.0	4.16	3.98	103.6	103.6
	S.D.	1.0	0.7	0.27	0.19	1.1	0.9
	n	5	5	5	5	5	5
<b>C B I</b> 0.5 mg/kg	Mean	145.2		4.08		104.0	
	S.D.	1.8		0.40		0.7	
	n	5		5		5	
<b>C B I</b> 5 mg/kg	Mean	145.6		4.26		104.2	
	S.D.	0.5		0.30		1.5	
	n	5		5		5	
<b>C B I</b> 50 mg/kg	Mean	145.8	146.0	4.32	3.92	104.8	104.2
	S.D.	1.6	0.7	0.15	0.11	1.5	1.6
	n	5	5	5	5	5	5

Significantly different from control : \*,P<0.05; \*\*,P<0.01.

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Table 13 Urinalysis - Summary

Male

Test Substance	pH	Male										Protein				Glucose				
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5 >= 9.0	-	+/-	1+	2+	3+	-	1+	2+	3+	4+	
Dose	Day 26										Day 26				Day 26					
C B I 0 mg/kg	n	0	0	0	0	0	0	1	4	0	0	3	2	0	0	5	0	0	0	
C B I 0.5 mg/kg	n	0	0	0	0	0	0	0	5	0	0	3	2	0	0	5	0	0	0	
C B I 5 mg/kg	n	0	0	0	0	0	0	0	5	0	1	0	4	0	0	5	0	0	0	
C B I 50 mg/kg	n	0	0	0	0	0	0	0	5	0	2	2	1	0	0	5	0	0	0	

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Study No. B081041

Table 13 Urinalysis - Summary

Male

Test Substance	Ketones					Occult Blood					
	-	+/-	Day 26	1+	2+	3+	-	+/-	Day 26	1+	2+
Dose											
CB 1											
0 mg/kg	n	0	2	3	0	0	4	0	1	0	0
CB 1											
0.5 mg/kg	n	0	3	2	0	0	5	0	0	0	0
CB 1											
5 mg/kg	n	1	2	2	0	0	4	1	0	0	0
CB 1											
50 mg/kg	n	2	2	1	0	0	5	0	0	0	0

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Study No. B081041

Table 13 Urinalysis - Summary

Female

Test Substance	pH								Protein				Glucose						
	5.0 Day 26		5.5	6.0	6.5	7.0	7.5	8.0	8.5 >= 9.0	-	+/- Day 26	1+	2+	3+	-	1+ Day 26	2+	3+	4+
Dose	n	0	0	0	0	0	0	2	3	0	4	0	1	0	0	5	0	0	0
CB 1 0 mg/kg	n	0	0	0	0	0	0	2	3	0	4	0	1	0	0	5	0	0	0
CB 1 0.5 mg/kg	n	0	0	0	0	0	0	0	5	0	2	0	3	0	0	5	0	0	0
CB 1 5 mg/kg	n	0	0	0	0	0	0	0	5	0	0	4	1	0	0	5	0	0	0
CB 1 50 mg/kg	n	0	0	0	0	0	0	2	3	0	3	0	2	0	0	5	0	0	0

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Table 13 Urinalysis - Summary

Female

Test Substance	Ketones						Occult Blood						
	-		+/-		1+	2+	3+	-		+/-		1+	2+
Dose	n	1	4	0	0	0	n	5	0	0	0	0	0
CB I 0 mg/kg	n	1	4	0	0	0	n	5	0	0	0	0	0
CB I 0.5 mg/kg	n	1	4	0	0	0	n	5	0	0	0	0	0
CB I 5 mg/kg	n	1	3	1	0	0	n	5	0	0	0	0	0
CB I 50 mg/kg	n	2	2	1	0	0	n	5	0	0	0	0	0

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Table 14 Organ Weight - Summary

Male

Test Substance	Final Body Weight		Brain		Thyroids		Thymus		Heart				
	Dose	g	Day 29	Day 43	g	Day 29	Day 43	mg	Day 29	Day 43	g	Day 29	Day 43
CB I	Mean	320.6	396.0	2.038	2.090	22.68	31.12	527.2	558.4	1.196	1.468		
0 mg/kg	S.D.	27.9	20.6	0.107	0.060	5.42	2.05	132.1	83.2	0.093	0.145		
	n	5	5	5	5	5	5	5	5	5	5		
CB I	Mean	326.6		1.974		21.80		584.6		1.110			
0.5 mg/kg	S.D.	30.1		0.052		4.18		101.7		0.091			
	n	5		5		5		5		5			
CB I	Mean	320.4		1.962		27.30		542.6		1.230			
5 mg/kg	S.D.	32.6		0.061		2.84		88.0		0.080			
	n	5		5		5		5		5			
CB I	Mean	258.0 *	365.0	1.902	2.008	26.70	29.04	415.6	554.4	0.982 *	1.378		
50 mg/kg	S.D.	27.7	24.6	0.069	0.174	5.62	4.04	94.4	103.7	0.142	0.087		
	n	5	5	5	5	5	5	5	5	5	5		
Test Substance													
Liver													
Dose	g		Day 29		Day 43		g		Day 29		g		
	CB I	Mean	9.378	10.994	0.674	0.742	2.624	3.112	56.74	57.96	3.228	3.450	
0 mg/kg	S.D.	0.990	0.393	0.096	0.151	0.178	0.338	10.27	8.35	0.088	0.322		
		n	5	5	5	5	5	5	5	5	5		
CB I	Mean	16.708 **		0.696		2.696		54.02		3.178			
0.5 mg/kg	S.D.	1.085		0.128		0.349		4.15		0.073			
		n	5		5		5		5		5		
CB I	Mean	24.988 **		0.778		2.908		50.22		3.320			
5 mg/kg	S.D.	2.217		0.118		0.350		3.48		0.185			
		n	5		5		5		5		5		
CB I	Mean	22.036 **	18.808 **	0.496	0.794	2.360	2.842	46.94	63.64	3.198	3.706		
50 mg/kg	S.D.	2.267	1.905	0.104	0.088	0.231	0.198	3.62	3.86	0.201	0.409		
		n	5	5	5	5	5	5	5	5	5		

Significantly different from control : \*P<0.05; \*\*P<0.01.

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Table 14 Organ Weight - Summary

Male

Test Substance	Epididymides		
	Dose	g	
		Day 29	Day 43
[REDACTED] C B I [REDACTED]	Mean	0.786	1.084
	S.D.	0.043	0.163
	n	5	5
[REDACTED] C B I [REDACTED]	Mean	0.752	
	S.D.	0.035	
	n	5	
[REDACTED] C B I [REDACTED]	Mean	0.734	
	S.D.	0.013	
	n	5	
[REDACTED] C B I [REDACTED]	Mean	0.716	1.056
	S.D.	0.059	0.102
	n	5	5

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Table 14 Organ Weight - Summary

Female

Test Substance	Final Body Weight		Brain		Thyroids		Thymus		Heart				
	Dose	g	Day 29	Day 43	g	Day 29	Day 43	mg	Day 29	Day 43	g	Day 29	Day 43
CB 1 0 mg/kg	Mean	216.4	242.4	1.890	1.918	18.42	21.32	532.6	497.2	0.876	0.984		
	S.D.	16.6	17.8	0.054	0.039	1.96	3.29	75.6	130.5	0.072	0.042		
	n	5	5	5	5	5	5	5	5	5	5		
CB 1 0.5 mg/kg	Mean	216.2		1.836		18.90		506.4		0.812			
	S.D.	23.6		0.064		1.84		63.4		0.100			
	n	5		5		5		5		5			
CB 1 5 mg/kg	Mean	216.0		1.828		19.92		507.2		0.886			
	S.D.	13.9		0.033		3.72		95.2		0.088			
	n	5		5		5		5		5			
CB 1 50 mg/kg	Mean	212.6	231.6	1.914	1.902	21.64	22.32	573.8	527.4	0.846	0.942		
	S.D.	9.4	20.4	0.078	0.084	4.79	4.69	145.4	111.1	0.065	0.094		
	n	5	5	5	5	5	5	5	5	5	5		
Test Substance													
		Liver		Spleen		Kidneys		Adrenals		Ovaries			
Dose	g	Day 29	Day 43	g	Day 29	Day 43	g	Day 29	Day 43	mg	Day 29	mg	Day 43
CB 1 0 mg/kg	Mean	6.814	7.150	0.508	0.532	1.684	1.720	66.74	68.68	91.12	95.88		
	S.D.	0.690	0.624	0.094	0.070	0.165	0.091	9.44	6.50	15.46	14.21		
	n	5	5	5	5	5	5	5	5	5	5		
CB 1 0.5 mg/kg	Mean	6.442		0.490		1.644		67.16		88.56			
	S.D.	0.913		0.060		0.205		11.48		14.53			
	n	5		5		5		5		5			
CB 1 5 mg/kg	Mean	7.148		0.506		1.686		65.64		95.40			
	S.D.	0.570		0.087		0.203		7.19		20.82			
	n	5		5		5		5		5			
CB 1 50 mg/kg	Mean	12.456 **	10.348 **	0.530	0.464	1.826	1.778	62.32	68.72	93.36	93.14		
	S.D.	0.971	0.866	0.095	0.089	0.124	0.126	8.09	6.80	6.73	11.98		
	n	5	5	5	5	5	5	5	5	5	5		

Significantly different from control : \*\*,P&lt;0.01.

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Table 15 Relative Organ Weight - Summary

Male

Test Substance	Final Body Weight		Brain		Thyroids		Thymus		Heart			
	Dose	g	%	Day 29	Day 43	x 10 <sup>-3</sup> %	Day 29	Day 43	x 10 <sup>-3</sup> %	Day 29	Day 43	%
C B I 0 mg/kg	Mean	320.6		396.0	0.638	0.530	7.10	7.90	163.90	141.70	0.374	0.374
	S.D.	27.9		20.6	0.058	0.020	1.81	0.91	35.68	25.63	0.011	0.050
	n	5		5	5	5	5	5	5	5	5	5
C B I 0.5 mg/kg	Mean	326.6			0.610		6.74		179.68		0.338 **	
	S.D.	30.1			0.048		1.39		29.75		0.008	
	n	5			5		5		5		5	
C B I 5 mg/kg	Mean	320.4			0.616		8.58		169.92		0.384	
	S.D.	32.6			0.058		1.11		26.79		0.021	
	n	5			5		5		5		5	
C B I 50 mg/kg	Mean	258.0 *		365.0	0.746 *	0.550	10.46 *	7.98	160.96	153.16	0.380	0.376
	S.D.	27.7		24.6	0.087	0.024	2.59	1.31	33.22	34.16	0.020	0.015
	n	5		5	5	5	5	5	5	5	5	5

Test Substance	Liver		Spleen		Kidneys		Adrenals		Testes			
	Dose	%	Day 29	Day 43	%	Day 29	Day 43	%	Day 29	Day 43	%	
C B I 0 mg/kg	Mean	2.922		2.776	0.210	0.188	0.818	0.782	17.64	14.64	1.012	0.870
	S.D.	0.118		0.053	0.027	0.042	0.044	0.051	2.45	2.11	0.103	0.039
	n	5		5	5	5	5	5	5	5	5	5
C B I 0.5 mg/kg	Mean	5.138 **			0.212		0.824		16.58		0.982	
	S.D.	0.406			0.024		0.042		1.42		0.112	
	n	5			5		5		5		5	
C B I 5 mg/kg	Mean	7.812 **			0.244		0.906		15.74		1.046	
	S.D.	0.308			0.030		0.059		1.21		0.119	
	n	5			5		5		5		5	
C B I 50 mg/kg	Mean	8.546 **		5.166 **	0.192	0.216	0.918 *	0.778	18.36	17.46 *	1.254 *	1.020
	S.D.	0.243		0.579	0.018	0.015	0.085	0.040	2.30	1.10	0.170	0.129
	n	5		5	5	5	5	5	5	5	5	5

Significantly different from control : \* , P&lt;0.05; \*\* , P&lt;0.01.

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Table 15 Relative Organ Weight - Summary

Male

Test Substance	Epididymides		
	Dose	%	
		Day 29	Day 43
CB 1 0 mg/kg	Mean	0.246	0.272
	S.D.	0.009	0.029
	n	5	5
CB 1 0.5 mg/kg	Mean	0.234	
	S.D.	0.030	
	n	5	
CB 1 5 mg/kg	Mean	0.232	
	S.D.	0.029	
	n	5	
CB 1 50 mg/kg	Mean	0.282	0.290
	S.D.	0.041	0.024
	n	5	5

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Table 15 Relative Organ Weight - Summary

Female

Test Substance	Final Body Weight		Brain		Thyroids		Thymus		Heart		
	g		%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43
Dose	Mean	S.D.	n	n	n	Mean	S.D.	n	Mean	S.D.	n
C B I 0 mg/kg	216.4	16.6	5	5	0.878	0.796	8.52	8.86	248.62	205.50	0.404
	S.D.				0.091	0.068	1.01	1.73	50.75	52.58	0.019
	n				5	5	5	5	5	5	5
C B I 0.5 mg/kg	216.2	23.6	5	5	0.856	0.100	8.84	1.44	236.98	42.77	0.374
	S.D.				5	5	5	5	5	5	0.011
	n										5
C B I 5 mg/kg	216.0	13.9	5	5	0.848	0.054	9.26	2.10	235.14	41.26	0.408
	S.D.				5	5	5	5	5	5	0.018
	n										5
C B I 50 mg/kg	212.6	9.4	5	5	0.900	0.038	10.12	9.58	269.78	67.46	0.396
	S.D.				5	5	5	5	5	5	0.026
	n										5
											0.023
Test Substance											
		Liver		Spleen		Kidneys		Adrenals		Ovaries	
Dose		%	Day 29	Day 43	%	Day 29	Day 43	%	x10 <sup>-3</sup> %	Day 29	x10 <sup>-3</sup> %
C B I 0 mg/kg	Mean	3.142	2.950	0.236	0.220	0.778	0.712	30.78	28.38	41.88	39.58
	S.D.	0.083	0.134	0.027	0.029	0.027	0.053	3.01	2.54	4.40	5.43
	n	5	5	5	5	5	5	5	5	5	5
C B I 0.5 mg/kg	Mean	2.972		0.228		0.762		30.94		40.82	
	S.D.	0.110		0.019		0.061		2.94		2.87	
	n	5		5		5		5		5	
C B I 5 mg/kg	Mean	3.310		0.232		0.778		30.32		43.94	
	S.D.	0.134		0.033		0.070		1.70		7.56	
	n	5		5		5		5		5	
C B I 50 mg/kg	Mean	5.854 **	4.476 **	0.250	0.200	0.860	0.772	29.30	29.76	44.00	40.22
	S.D.	0.271	0.257	0.043	0.029	0.045	0.028	3.62	3.06	3.92	3.81
	n	5	5	5	5	5	5	5	5	5	5

Significantly different from control : \*\*, P<0.01.

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Study No. B081041

Table 16 Necropsy Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance	Dose	Male				Female			
			0	0.5	5	50	0	0.5	5	50
		Dose Unit	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Liver		Number of Animals	5	5	5	5	5	5	5	5
Brownish change		Number of Animals Examined	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>
Enlargement			0	1	1	5	0	0	0	5
Whitish patch			0	0	1	3	0	0	0	0
Kidney			0	1	0	0	0	0	0	0
Dilatation, pelvis			0	0	0	0	0	0	0	0
Thyroid			0	0	0	0	0	0	0	2
Defect			0	0	0	0	0	0	0	2
Enlargement			0	0	0	0	0	0	0	2

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Table 17 Necropsy Findings - Summary

Scheduled sacrifice (Week 7)

Organ Findings	Sex	Male		Female	
	Test Substance	0	50	0	50
	Dose	CB I	CB I	CB I	CB I
	Dose Unit	mg/kg	mg/kg	mg/kg	mg/kg
	Number of Animals	5	5	5	5
	Number of Animals Examined	<5>	<5>	<5>	<5>
	Liver Enlargement	0	5	0	5
	Whitish patch	0	2	0	0
	Testis Asymmetry	0	1		
	Thyroid Nodule	0	1	0	0

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Table 18 Histological Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female				
		CB 1		CB 1		CB 1		CB 1		CB 1	
		0 mg/kg 5	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 5	0 mg/kg 5	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 5		
Grade		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Heart											
Ccell infiltration, lymphocyte, focal	1	1			1					0	
	2	0			0					0	
	3	0			0					0	
	4	0			0					0	
Lymph node, mandibular		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Lymph node, mesenteric		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Thymus		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Spleen		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Bone marrow, femur		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Trachea		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Lung (and bronchus)		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Accumulation, foam cell, focal	1	0			1					0	
	2	0			0					0	
	3	0			0					0	
	4	0			0					0	
Mineralization, arterial wall, focal	1	1			0					0	
	2	0			0					0	
	3	0			0					0	
	4	0			0					0	

<0> , Number of animals examined  
 1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

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Table 18 Histological Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female				
		C B I					C B I				
		0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg		0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	
Grade		5	5	5	5		5	5	5	5	
Stomach		<5>	<0>	<0>	<5>		<5>	<0>	<0>	<5>	
Cell infiltration, eosinophil, submucosa, focal	1	0			0		0			1	
	2	0			0		0			0	
	3	0			0		0			0	
	4	0			0		0			0	
Erosion, glandular stomach, focal	1	1			0		0			0	
	2	0			0		0			0	
	3	0			0		0			0	
	4	0			0		0			0	
Small intestine, duodenum		<5>	<0>	<0>	<5>		<5>	<0>	<0>	<5>	
Small intestine, jejunum		<5>	<0>	<0>	<5>		<5>	<0>	<0>	<5>	
Small intestine, ileum		<5>	<0>	<0>	<5>		<5>	<0>	<0>	<5>	
Large intestine, cecum		<5>	<0>	<0>	<5>		<5>	<0>	<0>	<5>	
Large intestine, colon		<5>	<0>	<0>	<5>		<5>	<0>	<0>	<5>	
Cell infiltration, lymphocyte, focal	1	0			0		1			0	
	2	0			0		0			0	
	3	0			0		0			0	
	4	0			0		0			0	
Large intestine, rectum		<5>	<0>	<0>	<5>		<5>	<0>	<0>	<5>	

<5> , Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

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Table 18 Histological Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance	Male								Female							
		CB 1				CB 1				CB 1				CB 1			
	Dose	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg
Dose Unit	mg/kg	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Number of Animals																	
Grade																	
Liver		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>
Brown pigment deposition, macrophage, focal	1	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cell infiltration, lymphocyte, focal	1	2	0	0	1	1	1	0	0	0	0	3	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Extramedullary hematopoiesis, erythrocytic	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Granuloma	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypertrophy, hepatocyte, centrilobular	1	0	5 **	5 **	0	**	0	0	0	0	0	0	5	0	0	0	**
	2	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

<5>, Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

Significantly different from control : \*\*, P<0.01.

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Table 18 Histological Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female				
		CB 1					CB 1				
		0 mg/kg 5	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 5	<5>	0 mg/kg 5	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 5	
Grade											
Liver		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	
Necrosis, hepatocyte, focal	1	0	1	3	4	*	0	0	0	0	3
	2	0	0	0	0		0	0	0	0	0
	3	0	0	0	0		0	0	0	0	0
	4	0	0	0	0		0	0	0	0	0
Kidney		<5>	<1>	<0>	<5>		<5>	<0>	<0>	<0>	
Basophilic tubule, proximal tubular epithelium	1	4	0		2		3				3
	2	0	0		0		0				0
	3	0	0		0		0				0
	4	0	0		0		0				0
Cell infiltration, lymphocyte, interstitium	1	0	0		1		0				0
	2	0	0		0		0				0
	3	0	0		0		0				0
	4	0	0		0		0				0
Dilatation, distal tubule	1	0	0		0		1				0
	2	0	0		0		0				0
	3	0	0		0		0				0
	4	0	0		0		0				0
Dilatation, pelvis	1	0	1		0		0				0
	2	0	0		0		0				0
	3	0	0		0		0				0
	4	0	0		0		0				0

<5>, Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

Significantly different from control : \* , P<0.05.

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Study No. B081041

Table 18 Histological Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female				
		C B I					C B I				
		0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	5 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	
Grade		<5>	<1>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Kidney											
Fibrosis, focal											
	1	0	0		0	0				1	
	2	0	0		0	0				0	
	3	0	0		0	0				0	
	4	0	0		0	0				0	
Urinary bladder		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Testis		<5>	<0>	<0>	<5>						
Epididymis		<5>	<0>	<0>	<5>						
Prostate		<5>	<0>	<0>	<5>						
Ovary							<5>	<0>	<0>	<5>	
Uterus							<5>	<0>	<0>	<5>	
Pituitary		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Thyroid		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	
Ectopic thymic tissue	1	1	0	0	0	0	0	0	0	0	
	2	0	0	0	0	0	0	0	0	0	
	3	0	0	0	0	0	0	0	0	0	
	4	0	0	0	0	0	0	0	0	0	

<> , Number of animals examined  
1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

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Table 18 Histological Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male					Female				
		C B I					C B I				
		0 mg/kg 5	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 5	0 mg/kg 5	0.5 mg/kg 5	5 mg/kg 5	50 mg/kg 5		
Grade		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>
Thyroid											
Hypertrophy, follicular cell	1	0	1	2	3	0	0	0	0	0	3
	2	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0
Ultimobranchial remnant	1	2	0	2	2	2	4	3	4		
	2	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0
Parathyroid		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>	
Adrenal		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>	
Accessory adrenocortical tissue	1	0	0	0	0	0	0	0	0	0	1
	2	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0
Hypertrophy, cortical cell, glomerular zone, diffuse	1	0	3	4 *	5 **	0	0	0	0	2	
	2	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0
Necrosis, cortical cell, focal	1	0	0	0	0	1	0	0	0	0	
	2	0	0	0	0	0	0	0	0	0	
	3	0	0	0	0	0	0	0	0	0	
	4	0	0	0	0	0	0	0	0	0	

<5>, Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

Significantly different from control : \*,P<0.05; \*\*,P<0.01.

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Table 18 Histological Findings - Summary

Scheduled sacrifice (Week 5)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Grade	Male				Female			
			0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg	0 mg/kg	0.5 mg/kg	5 mg/kg	50 mg/kg
			5	5	5	5	5	5	5	5
Brain		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>
Spinal cord		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>
Sciatic nerve		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>
Eyeball		<5>	<0>	<0>	<5>	<5>	<0>	<0>	<0>	<5>
Dysplasia, retina, focal		1 0			0	1				1
		2 0			0	0				0
		3 0			0	0				0
		4 0			0	0				0

<> , Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

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Table 19 Histological Findings - Summary

Scheduled sacrifice (Week 7)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male				Female			
		C B I		C B I		C B I		C B I	
		0 mg/kg	5 mg/kg	0 mg/kg	5 mg/kg	0 mg/kg	5 mg/kg	0 mg/kg	5 mg/kg
Grade		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>
Liver									
Brown pigment deposition, macrophage, focal	1	0	3	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Cell infiltration, lymphocyte, focal	1	2	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Extramedullary hematopoiesis, erythrocytic	1	0	1	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Hypertrophy, hepatocyte, centrilobular	1	0	5	**	0	5	**	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Necrosis, hepatocyte, focal	1	0	2	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0

<>, Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

Significantly different from control : \*\*,P<0.01.

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Table 19 Histological Findings - Summary

Scheduled sacrifice (Week 7)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male				Female			
		0	5	0	5	0	5	0	5
Grade									
Liver		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>
Proliferation, bile duct, focal	1	0	4	*	0	0	0	0	0
	2	0	0		0	0	0	0	0
	3	0	0		0	0	0	0	0
	4	0	0		0	0	0	0	0
Testis		<0>	<1>						
Dilatation, seminiferous tubule, diffuse	1		1						
	2		0						
	3		0						
	4		0						
Thyroid		<5>	<5>	<5>	<5>	<5>	<5>	<5>	<5>
Ectopic thymic tissue	1	0	1		0	0	0	0	0
	2	0	0		0	0	0	0	0
	3	0	0		0	0	0	0	0
	4	0	0		0	0	0	0	0
Hypertrophy, follicular cell	1	0	3		0	1			
	2	0	0		0	0	0	0	0
	3	0	0		0	0	0	0	0
	4	0	0		0	0	0	0	0
Ultimobranchial remnant	1	2	1		2	4			
	2	0	0		0	0	0	0	0
	3	0	0		0	0	0	0	0
	4	0	0		0	0	0	0	0

<> , Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

Significantly different from control : \*,P<0.05.

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Table 19 Histological Findings - Summary

Scheduled sacrifice (Week 7)

Organ Findings	Sex Test Substance Dose Dose Unit Number of Animals	Male		Female	
		CB	I	CB	I
		0	50	0	50
Adrenal	Grade	<5>	<5>	<5>	<5>
Hypertrophy, cortical cell, glomerular zone, diffuse	1	0	5	**	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	0	0

<> , Number of animals examined

1 , Minimal; 2 , Mild; 3 , Moderate; 4 , Severe

Significantly different from control : \*\*,P<0.01.

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Appendix 1 - 1 Clinical Sign		C B I		0 mg/kg		Male		Dosing period																		
Animal Number	Findings	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	10	20	10	20	10	20	10	20	10	20	
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20
20101	No Abnormality																									
20102	No Abnormality																									
20103	No Abnormality																									
20104	No Abnormality																									
20105	No Abnormality																									
20106	No Abnormality																									
20107	No Abnormality																									
20108	No Abnormality																									
20109	No Abnormality																									
20110	No Abnormality																									
Animal Number	Findings	Day	14	15	16	17	18	19	20	21	22	23	24	25	26	10	20	10	20	10	20	10	20	10	20	
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20
20101	No Abnormality																									
20102	No Abnormality																									
20103	No Abnormality																									
20104	No Abnormality																									
20105	No Abnormality																									
20106	No Abnormality																									
20107	No Abnormality																									
20108	No Abnormality																									
20109	No Abnormality																									
20110	No Abnormality																									

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 1 Clinical Sign      [ C B ]      0 mg/kg      Male      Dosing period

Animal Number	Findings	Day	27	28	29
		Time	10	20	10
20101	No Abnormality				
20102	No Abnormality				
20103	No Abnormality				
20104	No Abnormality				
20105	No Abnormality				
20106	No Abnormality				
20107	No Abnormality				
20108	No Abnormality				
20109	No Abnormality				
20110	No Abnormality				

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing;      Time 20 , After dosing;

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Appendix 1 - 2 Clinical Sign		C B I		0.5 mg/kg		Male		Dosing period																					
Animal Number	Findings	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	
20201	No Abnormality																												
20202	No Abnormality																												
20203	No Abnormality																												
20204	No Abnormality																												
20205	No Abnormality																												
Animal Number	Findings	Day	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29											
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20											
20201	No Abnormality																												
20202	No Abnormality																												
20203	No Abnormality																												
20204	No Abnormality																												
20205	No Abnormality																												
Animal Number	Findings	Day	27	28	29																								
		Time	10	20	10	20																							
20201	No Abnormality																												
20202	No Abnormality																												
20203	No Abnormality																												
20204	No Abnormality																												
20205	No Abnormality																												

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 3 Clinical Sign

[ C B I ] 5 mg/kg Male Dosing period

Animal Number	Findings	Day Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20
20301	No Abnormality																							
20302	No Abnormality																							
20303	No Abnormality																							
20304	No Abnormality																							
20305	No Abnormality																							
Animal Number	Findings	Day Time	14	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20
20301	No Abnormality																							
20302	No Abnormality																							
20303	No Abnormality																							
20304	No Abnormality																							
20305	No Abnormality																							
Animal Number	Findings	Day Time	27	20	10	20	28	10	20	29														
20301	No Abnormality																							
20302	No Abnormality																							
20303	No Abnormality																							
20304	No Abnormality																							
20305	No Abnormality																							

+, Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
 Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 4 Clinical Sign

C B I 50 mg/kg Male Dosing period

Animal Number	Findings	Day Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20
20401	No Abnormality																									
20402	No Abnormality																									
20403	No Abnormality																									
20404	No Abnormality																									
20405	No Abnormality																									
20406	No Abnormality																									
20407	No Abnormality																									
20408	No Abnormality																									
20409	No Abnormality																									
20410	No Abnormality																									
Animal Number	Findings	Day Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20
20401	No Abnormality																									
20402	No Abnormality																									
20403	No Abnormality																									
20404	No Abnormality																									
20405	No Abnormality																									
20406	No Abnormality																									
20407	No Abnormality																									
20408	No Abnormality																									
20409	No Abnormality																									
20410	No Abnormality																									

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;

Time 10 , Before dosing; Time 20 , After dosing;

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Appendix I - 4 Clinical Sign       50 mg/kg      Male      Dosing period

Animal Number	Findings	Day	27	28	29
		Time	10	20	10
20401	No Abnormality				
20402	No Abnormality				
20403	No Abnormality				
20404	No Abnormality				
20405	No Abnormality				
20406	No Abnormality				
20407	No Abnormality				
20408	No Abnormality				
20409	No Abnormality				
20410	No Abnormality				

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing;      Time 20 , After dosing;

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Appendix 1 - 5 Clinical Sign		C B I		0 mg/kg		Female		Dosing period											
Animal Number	Findings	Day Time	10 20	2 10 20	3 10 20	4 10 20	5 10 20	6 10 20	7 10 20	8 10 20	9 10 20	10 10 20	11 10 20	12 10 20	13 10 20				
60101	No Abnormality																		
60102	No Abnormality																		
60103	No Abnormality																		
60104	No Abnormality																		
60105	No Abnormality																		
60106	No Abnormality																		
60107	No Abnormality																		
60108	No Abnormality																		
60109	No Abnormality																		
60110	No Abnormality																		
Animal Number	Findings	Day Time	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20	10 20		
60101	No Abnormality																		
60102	No Abnormality																		
60103	No Abnormality																		
60104	No Abnormality																		
60105	No Abnormality																		
60106	No Abnormality																		
60107	No Abnormality																		
60108	No Abnormality																		
60109	No Abnormality																		
60110	No Abnormality																		

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 5 Clinical Sign		C B I		0 mg/kg		Female	Dosing period
Animal Number	Findings	Day Time	27 10	28 20	29 10		
60101	No Abnormality						
60102	No Abnormality						
60103	No Abnormality						
60104	No Abnormality						
60105	No Abnormality						
60106	No Abnormality						
60107	No Abnormality						
60108	No Abnormality						
60109	No Abnormality						
60110	No Abnormality						

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 6 Clinical Sign		C B		0.5 mg/kg		Female		Dosing period																					
Animal Number	Findings	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	
60201	No Abnormality																												
60202	No Abnormality																												
60203	No Abnormality																												
60204	No Abnormality																												
60205	No Abnormality																												
Animal Number	Findings	Day	14	15	16	17	18	19	20	21	22	23	24	25	26	10	20	10	20	10	20	10	20	10	20	10	20	10	20
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	
60201	No Abnormality																												
60202	No Abnormality																												
60203	No Abnormality																												
60204	No Abnormality																												
60205	No Abnormality																												
Animal Number	Findings	Day	27	28	29											10	20	10	20										
		Time	10	20	10	20																							
60201	No Abnormality																												
60202	No Abnormality																												
60203	No Abnormality																												
60204	No Abnormality																												
60205	No Abnormality																												

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 7 Clinical Sign		C B I		5 mg/kg		Female		Dosing period																													
Animal Number	Findings	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29						
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20					
60301	No Abnormality																																				
60302	No Abnormality																																				
60303	No Abnormality																																				
60304	No Abnormality																																				
60305	No Abnormality																																				
Animal Number	Findings	Day	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	10	20	10	20	10	20	10	20	10	20	10	20	10	20					
		Time	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20					
60301	No Abnormality																																				
60302	No Abnormality																																				
60303	No Abnormality																																				
60304	No Abnormality																																				
60305	No Abnormality																																				
Animal Number	Findings	Day	27	28	29																																
		Time	10	20	10	20																															
60301	No Abnormality																																				
60302	No Abnormality																																				
60303	No Abnormality																																				
60304	No Abnormality																																				
60305	No Abnormality																																				

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 8 Clinical Sign		C B I		50 mg/kg		Female		Dosing period																			
Animal Number	Findings	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	Time	10	20	10	20	10	20	10	20	10	20	
60401	No Abnormality																										
60402	No Abnormality																										
60403	No Abnormality																										
60404	No Abnormality																										
60405	No Abnormality																										
60406	No Abnormality																										
60407	No Abnormality																										
60408	No Abnormality																										
60409	No Abnormality																										
60410	No Abnormality																										
Animal Number	Findings	Day	14	15	16	17	18	19	20	21	22	23	24	25	26	Time	10	20	10	20	10	20	10	20	10	20	
60401	No Abnormality																										
60402	No Abnormality																										
60403	No Abnormality																										
60404	No Abnormality																										
60405	No Abnormality																										
60406	No Abnormality																										
60407	No Abnormality																										
60408	No Abnormality																										
60409	No Abnormality																										
60410	No Abnormality																										

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 1 - 8 Clinical Sign		C B I	50 mg/kg	Female	Dosing period
Animal Number	Findings	Day	27	28	29
		Time	10	20	10
60401	No Abnormality				
60402	No Abnormality				
60403	No Abnormality				
60404	No Abnormality				
60405	No Abnormality				
60406	No Abnormality				
60407	No Abnormality				
60408	No Abnormality				
60409	No Abnormality				
60410	No Abnormality				

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;  
Time 10 , Before dosing; Time 20 , After dosing;

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Appendix 2 - 1 Clinical Sign

C B I 0 mg/kg

Male

Recovery period

Animal Number	Findings	Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
		Time	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
20106	No Abnormality																
20107	No Abnormality																
20108	No Abnormality																
20109	No Abnormality																
20110	No Abnormality																

+, Present; 1 , Slight; 2 , Moderate; 3 , Severe;

Time 10 , Once a day;

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Study No. B081041

Appendix 2 - 2 Clinical Sign      **C B I**    50 mg/kg    Male    Recovery period

Animal Number	Findings	Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
		Time	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
20406	No Abnormality																
20407	No Abnormality																
20408	No Abnormality																
20409	No Abnormality																
20410	No Abnormality																

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;

Time 10 , Once a day;

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Study No. B081041

Appendix 2 - 3 Clinical Sign      **C B I**      0 mg/kg      Female      Recovery period

Animal Number	Findings	Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
		Time	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
60106	No Abnormality																
60107	No Abnormality																
60108	No Abnormality																
60109	No Abnormality																
60110	No Abnormality																

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;

Time 10 , Once a day;

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Appendix 2 - 4 Clinical Sign

C B I 50 mg/kg

Female

Recovery period

Animal Number	Findings	Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
		Time	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
60406	No Abnormality																
60407	No Abnormality																
60408	No Abnormality																
60409	No Abnormality																
60410	No Abnormality																

+ , Present; 1 , Slight; 2 , Moderate; 3 , Severe;

Time 10 , Once a day;

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Study No. B081041

Appendix 3 - 1    Detailed Clinical Observations    Stage : Week -1    0 mg/kg    Male

Items	Animal Number	20101	20102	20103	20104	20105	20106	20107	20108	20109	20110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	3	8	11	6	12	7	8	11	9	10	
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	N	P	P	N	P	P	N	P	P	P	N
Defecation	P	N	N	N	P	N	N	N	N	N	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Study No. B081041

Appendix 3 - 2    Detailed Clinical Observations    Stage : Week -1    0.5 mg/kg    Male

Items	Animal Number	20201	20202	20203	20204	20205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		I	I	I	I	I
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		10	3	6	7	7
Arousal		3	3	3	3	3
Urination		P	P	N	P	N
Defecation		P	P	N	N	P
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 3 - 3    Detailed Clinical Observations    Stage : Week -1    5 mg/kg    Male

Items	Animal Number	20301	20302	20303	20304	20305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacration	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	2	6	10	16	8	
Arousal	3	3	3	3	3	
Urination	P	P	N	P	N	
Defecation	N	P	N	N	N	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 3 - 4    Detailed Clinical Observations    Stage : Week -1    50 mg/kg    Male

Items	Animal Number	20401	20402	20403	20404	20405	20406	20407	20408	20409	20410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	I	I	I	I	I	I	I	I	I	I	I
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacration	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	4	9	5	8	4	4	11	3	14	2	
Arousal	3	3	3	3	3	3	3	3	3	3	
Urination	P	P	P	P	P	N	N	N	P	P	
Defecation	N	P	N	P	N	N	N	N	P	P	
Posture, body position	N	N	N	N	N	N	N	N	N	N	
Breathing	N	N	N	N	N	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	
Gait	N	N	N	N	N	N	N	N	N	N	
Tremor	N	N	N	N	N	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	
Stereotypy	N	N	N	N	N	N	N	N	N	N	
<u>Bizarre behaviour</u>	N	N	N	N	N	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 3 - 5    Detailed Clinical Observations    Stage : Week -1    0 mg/kg    Female

Items	Animal Number	60101	60102	60103	60104	60105	60106	60107	60108	60109	60110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacration		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		2	2	7	6	5	4	4	2	6	11
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	P	P	N	N	N	N	N	N	N
Defecation		N	N	N	N	N	N	N	N	N	P
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 3 - 6    Detailed Clinical Observations    Stage : Week -1    0.5 mg/kg    Female

Items	Animal Number	60201	60202	60203	60204	60205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		I	I	I	I	I
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		5	5	5	4	2
Arousal		3	3	3	3	3
Urination		N	N	N	N	N
Defecation		N	N	N	P	N
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 3 - 7    Detailed Clinical Observations    Stage : Week -1    5 mg/kg    Female

Items	Animal Number	60301	60302	60303	60304	60305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacration	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	4	5	6	4	8	
Arousal	3	3	3	3	3	
Urination	N	N	N	N	P	
Defecation	N	N	N	N	P	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
<u>Bizarre behaviour</u>	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 3 - 8    Detailed Clinical Observations    Stage : Week -1    50 mg/kg    Female

Items	Animal Number	60401	60402	60403	60404	60405	60406	60407	60408	60409	60410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		I	I	I	I	I	I	I	I	I	I
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacration		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		4	8	2	2	3	13	3	6	8	1
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	N	P	P	N	N	P	N	N	N
Defecation		N	N	N	N	N	N	N	N	N	N
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 4 - 1    Detailed Clinical Observations    Stage : Week 1    0 mg/kg    Male

Items	Animal Number	20101	20102	20103	20104	20105	20106	20107	20108	20109	20110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacration		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		2	2	4	3	0	0	6	2	1	4
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	N	N	N	P	N	P	P	N	N
Defecation		P	P	N	N	N	P	P	P	P	N
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 4 - 2    Detailed Clinical Observations    Stage : Week 1    0.5 mg/kg    Male

Items	Animal Number	20201	20202	20203	20204	20205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	I	I	I	I	I	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	0	1	I	0	0	0
Arousal	3	3	3	3	3	3
Urination	P	N	P	P	P	P
Defecation	P	N	P	P	P	P
Posture, body position	N	N	N	N	N	N
Breathing	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N
Gait	N	N	N	N	N	N
Tremor	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 4 - 3    Detailed Clinical Observations    Stage : Week 1    5 mg/kg    Male

Items	Animal Number	20301	20302	20303	20304	20305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		1	1	1	1	1
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		2	0	2	0	1
Arousal		3	3	3	3	3
Urination		N	N	N	N	P
Defecation		N	P	N	P	N
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 4 - 4      Detailed Clinical Observations      Stage : Week 1      50 mg/kg      Male

Items	Animal Number	20401	20402	20403	20404	20405	20406	20407	20408	20409	20410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		I	I	I	I	I	I	I	I	I	I
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacrimation		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		2	0	8	6	1	4	4	2	0	2
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	N	N	N	P	P	N	N	P	N
Defecation		N	P	P	P	N	N	P	N	P	N
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 4 - 5    Detailed Clinical Observations    Stage : Week 1    0 mg/kg    Female

Items	Animal Number	60101	60102	60103	60104	60105	60106	60107	60108	60109	60110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacration		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		2	4	11	0	3	14	4	0	4	14
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	N	N	N	N	P	N	P	P	N
Defecation		P	N	N	P	P	P	N	P	N	N
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 4 - 6    Detailed Clinical Observations    Stage : Week 1    0.5 mg/kg    Female

Items	Animal Number	60201	60202	60203	60204	60205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		1	1	1	1	1
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacration		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		5	4	20	2	0
Arousal		3	3	3	3	3
Urination		N	P	N	N	N
Defecation		N	P	N	N	P
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 4 - 7    Detailed Clinical Observations    Stage : Week 1    5 mg/kg    Female

Items	Animal Number	60301	60302	60303	60304	60305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	I	I	I	I	I	I
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	12	1	6	6	5	
Arousal	3	3	3	3	3	
Urination	N	N	N	N	N	
Defecation	N	N	N	N	P	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 4 - 8    Detailed Clinical Observations    Stage : Week 1    50 mg/kg    Female

Items	Animal Number	60401	60402	60403	60404	60405	60406	60407	60408	60409	60410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	6	1	2	0	4	6	0	4	11	2	
Arousal	3	3	3	3	3	3	3	3	3	3	
Urination	N	N	N	N	N	N	N	N	P	N	
Defecation	N	P	N	N	N	N	P	N	P	N	
Posture, body position	N	N	N	N	N	N	N	N	N	N	
Breathing	N	N	N	N	N	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	
Gait	N	N	N	N	N	N	N	N	N	N	
Tremor	N	N	N	N	N	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	
Stereotypy	N	N	N	N	N	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	

See Annex 11.2 for details of criteria

## CONFIDENTIAL

Study No. B081041

Appendix 5 - 1    Detailed Clinical Observations    Stage : Week 2    0 mg/kg    Male

Items	Animal Number	20101	20102	20103	20104	20105	20106	20107	20108	20109	20110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	I	I	I	I	I	I	I	I	I	I	I
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacration	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	0	0	8	3	0	0	0	3	5	0	
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	P	P	N	N	N	P	P	N	N	N	N
Defecation	P	P	N	N	N	N	N	P	P	P	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 5 - 2    Detailed Clinical Observations    Stage : Week 2    0.5 mg/kg    Male

Items	Animal Number	20201	20202	20203	20204	20205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	I	I	I	I	I	I
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacration	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	0	0	0	1	6	
Arousal	3	3	3	3	3	
Urination	P	P	N	N	N	
Defecation	P	N	N	N	N	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 5 - 3    Detailed Clinical Observations    Stage : Week 2    5 mg/kg    Male

Items	Animal Number	20301	20302	20303	20304	20305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacration	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	0	0	0	1	1	
Arousal	3	3	3	3	3	
Urination	N	N	P	P	P	N
Defecation	N	P	P	P	P	N
Posture, body position	N	N	N	N	N	N
Breathing	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N
Gait	N	N	N	N	N	N
Tremor	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 5 - 4    Detailed Clinical Observations    Stage : Week 2    50 mg/kg    Male

Items	Animal Number	20401	20402	20403	20404	20405	20406	20407	20408	20409	20410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacration	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	0	0	8	1	0	0	0	0	0	0	0
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	N	P	P	P	N	P	P	N	P	N	N
Defecation	N	P	P	P	N	P	P	N	P	N	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 5 - 5 Detailed Clinical Observations Stage : Week 2 0 mg/kg Female

Items	Animal Number	60101	60102	60103	60104	60105	60106	60107	60108	60109	60110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		I	I	I	I	I	I	I	I	I	I
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacration		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		0	8	6	7	0	13	2	5	9	4
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	N	P	N	P	N	N	N	N	N
Defecation		P	N	N	N	N	N	N	N	N	P
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 5 - 6    Detailed Clinical Observations    Stage : Week 2    0.5 mg/kg    Female

Items	Animal Number	60201	60202	60203	60204	60205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		1	1	1	1	1
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		8	2	10	4	1
Arousal		3	3	3	3	3
Urination		N	N	N	P	N
Defecation		N	P	N	N	P
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 5 - 7    Detailed Clinical Observations    Stage : Week 2    5 mg/kg    Female

Items	Animal Number	60301	60302	60303	60304	60305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		1	1	1	1	1
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		3	3	3	3	9
Arousal		3	3	3	3	3
Urination		P	P	N	N	P
Defecation		N	N	N	N	P
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 5 - 8    Detailed Clinical Observations    Stage : Week 2    50 mg/kg    Female

Items	Animal Number	60401	60402	60403	60404	60405	60406	60407	60408	60409	60410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacration	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	8	8	4	2	5	6	2	2	4	0	
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	P	N	N	P	N	P	N	N	N	N	N
Defecation	N	N	N	N	N	N	N	N	N	N	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Study No. B081041

Appendix 6 - 1    Detailed Clinical Observations    Stage : Week 3    0 mg/kg    Male

Items	Animal Number	20101	20102	20103	20104	20105	20106	20107	20108	20109	20110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacration	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	0	0	5	1	1	0	6	0	7	0	0
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	N	P	N	N	N	N	N	P	P	P	N
Defecation	N	P	N	P	N	N	N	P	P	P	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Study No. B081041

Appendix 6 - 2    Detailed Clinical Observations    Stage : Week 3    0.5 mg/kg    Male

Items	Animal Number	20201	20202	20203	20204	20205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacration	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	5	1	1	0	4	
Arousal	3	3	3	3	3	
Urination	N	P	N	N	N	
Defecation	P	N	P	P	N	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 6 - 3    Detailed Clinical Observations    Stage : Week 3    5 mg/kg    Male

Items	Animal Number	20301	20302	20303	20304	20305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		1	1	1	1	1
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		4	2	1	1	3
Arousal		3	3	3	3	3
Urination		N	P	N	N	N
Defecation		N	P	P	P	N
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 6 - 4    Detailed Clinical Observations    Stage : Week 3    50 mg/kg    Male

Items	Animal Number	20401	20402	20403	20404	20405	20406	20407	20408	20409	20410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	0	0	9	6	0	1	4	0	2	1	
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	N	P	P	N	N	N	P	P	N	P	N
Defecation	N	P	P	N	N	N	P	P	N	P	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 6 - 5 Detailed Clinical Observations Stage : Week 3 0 mg/kg Female

Items	Animal Number	60101	60102	60103	60104	60105	60106	60107	60108	60109	60110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacration		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		1	2	6	5	7	4	8	0	4	1
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	N	N	N	N	N	N	N	N	N
Defecation		P	N	N	N	N	N	N	N	N	P
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 6 - 6    Detailed Clinical Observations    Stage : Week 3    0.5 mg/kg    Female

Items	Animal Number	60201	60202	60203	60204	60205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacration	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	4	0	11	4	1	
Arousal	3	3	3	3	3	
Urination	P	P	P	P	P	
Defecation	N	N	N	N	P	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 6 - 7    Detailed Clinical Observations    Stage : Week 3    5 mg/kg    Female

Items	Animal Number	60301	60302	60303	60304	60305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	3	2	3	1	7	
Arousal	3	3	3	3	3	
Urination	P	N	N	N	P	
Defecation	N	N	N	N	P	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 6 - 8    Detailed Clinical Observations    Stage : Week 3    50 mg/kg    Female

Items	Animal Number	60401	60402	60403	60404	60405	60406	60407	60408	60409	60410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacration	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	12	5	0	2	0	8	2	3	8	13	
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	N	N	P	N	N	N	P	N	N	N	N
Defecation	N	N	N	N	N	N	N	N	N	N	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 7 - 1    Detailed Clinical Observations    Stage : Week 4    0 mg/kg    Male

Items	Animal Number	20101	20102	20103	20104	20105	20106	20107	20108	20109	20110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	N	N
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		1	1	1	1	1	1	1	1	1	1
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacrimation		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		0	0	8	0	7	6	1	0	4	0
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	P	N	N	N	P	N	P	P	N
Defecation		N	P	P	N	N	N	N	P	P	N
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 7 - 2    Detailed Clinical Observations    Stage : Week 4    0.5 mg/kg    Male

Items	Animal Number	20201	20202	20203	20204	20205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		1	1	1	1	1
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		6	1	1	0	2
Arousal		3	3	3	3	3
Urination		N	N	N	N	N
Defecation		N	P	P	P	N
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 7 - 3    Detailed Clinical Observations    Stage : Week 4    5 mg/kg    Male

Items	Animal Number	20301	20302	20303	20304	20305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		I	I	I	I	I
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		11	3	2	0	5
Arousal		3	3	3	3	3
Urination		N	N	N	N	P
Defecation		N	P	N	P	P
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 7 - 4    Detailed Clinical Observations    Stage : Week 4    50 mg/kg    Male

Items	Animal Number	20401	20402	20403	20404	20405	20406	20407	20408	20409	20410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacrimation	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	0	3	5	14	6	5	4	2	5	2	
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	N	P	N	N	N	P	N	N	N	P	N
Defecation	N	P	P	N	N	N	N	N	N	N	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 7 - 5    Detailed Clinical Observations    Stage : Week 4    0 mg/kg    Female

Items	Animal Number	60101	60102	60103	60104	60105	60106	60107	60108	60109	60110
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression		N	N	N	N	N	N	N	N	N	N
Trauma		N	N	N	N	N	N	N	N	N	N
Color of skin		N	N	N	N	N	N	N	N	N	N
Soiled fur		N	N	N	N	N	N	N	N	N	N
Exophthalmos		N	N	N	N	N	N	N	N	N	N
Palpebral closure		I	I	I	I	I	I	I	I	I	I
Color of conjunctiva		N	N	N	N	N	N	N	N	N	N
Secretion		N	N	N	N	N	N	N	N	N	N
Lacrimation		N	N	N	N	N	N	N	N	N	N
Salivation		N	N	N	N	N	N	N	N	N	N
Piloerection		N	N	N	N	N	N	N	N	N	N
Pupil size		N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing		1	6	11	8	8	14	9	5	2	3
Arousal		3	3	3	3	3	3	3	3	3	3
Urination		N	P	N	N	P	N	N	N	N	N
Defecation		N	N	N	N	N	N	N	N	N	P
Posture, body position		N	N	N	N	N	N	N	N	N	N
Breathing		N	N	N	N	N	N	N	N	N	N
Co-ordination movement		N	N	N	N	N	N	N	N	N	N
Gait		N	N	N	N	N	N	N	N	N	N
Tremor		N	N	N	N	N	N	N	N	N	N
Clonic convulsion		N	N	N	N	N	N	N	N	N	N
Tonic convulsion		N	N	N	N	N	N	N	N	N	N
Stereotypy		N	N	N	N	N	N	N	N	N	N
Bizarre behaviour		N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 7 - 6    Detailed Clinical Observations    Stage : Week 4    0.5 mg/kg    Female

Items	Animal Number	60201	60202	60203	60204	60205
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression		N	N	N	N	N
Trauma		N	N	N	N	N
Color of skin		N	N	N	N	N
Soiled fur		N	N	N	N	N
Exophthalmos		N	N	N	N	N
Palpebral closure		1	1	1	1	1
Color of conjunctiva		N	N	N	N	N
Secretion		N	N	N	N	N
Lacrimation		N	N	N	N	N
Salivation		N	N	N	N	N
Piloerection		N	N	N	N	N
Pupil size		N	N	N	N	N
Open field observations						
Rearing		6	1	15	7	1
Arousal		3	3	3	3	3
Urination		N	P	N	N	P
Defecation		N	P	N	N	P
Posture, body position		N	N	N	N	N
Breathing		N	N	N	N	N
Co-ordination movement		N	N	N	N	N
Gait		N	N	N	N	N
Tremor		N	N	N	N	N
Clonic convulsion		N	N	N	N	N
Tonic convulsion		N	N	N	N	N
Stereotypy		N	N	N	N	N
Bizarre behaviour		N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 7 - 7    Detailed Clinical Observations    Stage : Week 4    5 mg/kg    Female

Items	Animal Number	60301	60302	60303	60304	60305
Hand-held observations						
Reactivity on removal from the cage		2	2	2	2	2
Reactivity to handling		2	2	2	2	2
Aggression	N	N	N	N	N	N
Trauma	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N
Secretion	N	N	N	N	N	N
Lacration	N	N	N	N	N	N
Salivation	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N
Open field observations						
Rearing	10	4	8	4	8	
Arousal	3	3	3	3	3	
Urination	N	P	P	N	P	
Defecation	N	N	N	N	P	
Posture, body position	N	N	N	N	N	
Breathing	N	N	N	N	N	
Co-ordination movement	N	N	N	N	N	
Gait	N	N	N	N	N	
Tremor	N	N	N	N	N	
Clonic convulsion	N	N	N	N	N	
Tonic convulsion	N	N	N	N	N	
Stereotypy	N	N	N	N	N	
Bizarre behaviour	N	N	N	N	N	

See Annex 11.2 for details of criteria

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Appendix 7 - 8    Detailed Clinical Observations    Stage : Week 4    50 mg/kg    Female

Items	Animal Number	60401	60402	60403	60404	60405	60406	60407	60408	60409	60410
Hand-held observations											
Reactivity on removal from the cage		2	2	2	2	2	2	2	2	2	2
Reactivity to handling		2	2	2	2	2	2	2	2	2	2
Aggression	N	N	N	N	N	N	N	N	N	N	N
Trauma	N	N	N	N	N	N	N	N	N	N	N
Color of skin	N	N	N	N	N	N	N	N	N	N	N
Soiled fur	N	N	N	N	N	N	N	N	N	N	N
Exophthalmos	N	N	N	N	N	N	N	N	N	N	N
Palpebral closure	1	1	1	1	1	1	1	1	1	1	1
Color of conjunctiva	N	N	N	N	N	N	N	N	N	N	N
Secretion	N	N	N	N	N	N	N	N	N	N	N
Lacration	N	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N	N
Piloerection	N	N	N	N	N	N	N	N	N	N	N
Pupil size	N	N	N	N	N	N	N	N	N	N	N
Open field observations											
Rearing	7	6	5	8	0	3	6	0	1	4	
Arousal	3	3	3	3	3	3	3	3	3	3	3
Urination	N	N	N	N	N	P	N	N	P	P	N
Defecation	N	N	N	N	N	P	N	N	N	N	N
Posture, body position	N	N	N	N	N	N	N	N	N	N	N
Breathing	N	N	N	N	N	N	N	N	N	N	N
Co-ordination movement	N	N	N	N	N	N	N	N	N	N	N
Gait	N	N	N	N	N	N	N	N	N	N	N
Tremor	N	N	N	N	N	N	N	N	N	N	N
Clonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Tonic convulsion	N	N	N	N	N	N	N	N	N	N	N
Stereotypy	N	N	N	N	N	N	N	N	N	N	N
Bizarre behaviour	N	N	N	N	N	N	N	N	N	N	N

See Annex 11.2 for details of criteria

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Appendix 8 - 1    Function Tests                          Stage : Week 4    0 mg/kg                          Male

Items	Animal Number	20101	20102	20103	20104	20105	20106	20107	20108	20109	20110
Sensory reactivity to stimuli											
Approach response		2	2	2	2	2	2	2	2	2	2
Touch response		2	2	2	2	2	3	2	2	2	2
Auditory response		2	2	2	2	2	2	2	2	2	2
Tail pinch response		2	2	2	2	2	2	2	2	2	2
Aerial righting reaction		1	1	1	1	1	1	1	1	1	1
Grip strength											
Forelimb (g)		563	905	897	756	896	898	933	888	954	722
Hindlimb (g)		501	610	825	568	572	634	618	510	691	567

See Annex 11.2 for details of criteria

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Appendix 8 - 2    Function Tests              Stage : Week 4    0.5 mg/kg              Male

Items	Animal Number	20201	20202	20203	20204	20205
Sensory reactivity to stimuli						
Approach response		2	2	2	2	2
Touch response		2	2	2	2	2
Auditory response		2	2	2	2	2
Tail pinch response		2	2	2	2	2
Aerial righting reaction		1	1	1	1	1
Grip strength						
Forelimb (g)		948	1096	1021	856	814
Hindlimb (g)		608	617	726	702	543

See Annex 11.2 for details of criteria

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Appendix 8 - 3    Function Tests                      Stage : Week 4    5 mg/kg                      Male

Items	Animal Number	20301	20302	20303	20304	20305
Sensory reactivity to stimuli						
Approach response		2	2	2	2	2
Touch response		2	2	3	2	2
Auditory response		2	2	2	2	2
Tail pinch response		2	2	2	2	2
Aerial righting reaction		1	1	1	1	1
Grip strength						
Forelimb (g)		874	841	951	700	961
Hindlimb (g)		477	496	730	701	727

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Appendix 8 - 4	Function Tests	Stage : Week 4	50 mg/kg	Male								
Items		Animal Number	20401	20402	20403	20404	20405	20406	20407	20408	20409	20410
Sensory reactivity to stimuli												
Approach response			2	2	2	2	2	2	2	2	2	2
Touch response			2	2	2	2	3	2	2	2	2	2
Auditory response			2	2	2	2	2	2	2	2	2	2
Tail pinch response			2	2	2	2	2	2	2	2	2	2
Aerial righting reaction			1	1	1	1	1	1	1	1	1	1
Grip strength												
Forelimb (g)			897	749	622	803	838	788	836	659	938	784
Hindlimb (g)			485	588	370	598	680	486	714	447	504	715

See Annex 11.2 for details of criteria

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Appendix 8 - 5      Function Tests	Stage : Week 4	0 mg/kg	Female								
Items	Animal Number	60101	60102	60103	60104	60105	60106	60107	60108	60109	60110
Sensory reactivity to stimuli											
Approach response		2	2	2	2	2	2	2	2	2	2
Touch response		2	2	2	2	2	2	2	2	2	2
Auditory response		2	2	2	2	2	2	2	2	2	2
Tail pinch response		2	2	2	2	2	2	2	2	2	2
Aerial righting reaction		1	1	1	1	1	1	1	1	1	1
Grip strength											
Forelimb (g)		767	562	799	888	1010	627	778	644	804	673
Hindlimb (g)		568	503	599	599	542	666	547	435	572	555

See Annex 11.2 for details of criteria

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Appendix 8 - 6 Function Tests      Stage : Week 4      0.5 mg/kg      Female

Items	Animal Number	60201	60202	60203	60204	60205
Sensory reactivity to stimuli						
Approach response		2	2	2	2	2
Touch response		2	2	2	2	3
Auditory response		2	2	2	2	2
Tail pinch response		2	2	2	2	2
Aerial righting reaction		1	1	1	1	1
Grip strength						
Forelimb (g)		689	821	749	740	867
Hindlimb (g)		538	638	602	527	472

See Annex 11.2 for details of criteria

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Appendix 8 - 7      Function Tests	Stage : Week 4	5 mg/kg	Female			
Items	Animal Number	60301	60302	60303	60304	60305
Sensory reactivity to stimuli						
Approach response		2	2	2	2	2
Touch response		2	2	2	2	2
Auditory response		2	2	2	2	2
Tail pinch response		2	2	2	2	2
Aerial righting reaction		1	1	1	1	1
Grip strength						
Forelimb (g)		746	877	665	657	704
Hindlimb (g)		604	474	424	464	604

See Annex 11.2 for details of criteria

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Appendix 8 - 8      Function Tests	Stage : Week 4	50 mg/kg	Female								
Items	Animal Number	60401	60402	60403	60404	60405	60406	60407	60408	60409	60410
Sensory reactivity to stimuli											
Approach response		2	2	2	2	2	2	2	2	2	2
Touch response		2	2	2	2	2	2	3	2	2	3
Auditory response		2	2	2	2	2	2	2	2	2	2
Tail pinch response		2	2	2	2	2	2	2	2	2	2
Aerial righting reaction		1	1	1	1	1	1	1	1	1	1
Grip strength											
Forelimb (g)		613	910	761	690	758	810	884	682	782	750
Hindlimb (g)		645	622	459	463	497	424	559	508	379	504

See Annex 11.2 for details of criteria

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Appendix 9 - 1      Motor Activity      Stage : Week 4      0 mg/kg      Male

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
20101		2098	1152	182	81	102	54	3669
20102		1848	1939	1282	4	32	13	5118
20103		2454	1364	31	13	108	70	4040
20104		2788	2235	658	5	0	62	5748
20105		2624	2338	395	2	30	42	5431
20106		1951	2705	2000	2512	62	260	9490
20107		2647	1366	226	1	555	65	4860
20108		1873	2546	955	2303	5	1064	8746
20109		1668	1618	9	16	4	149	3464
20110		1855	1502	170	97	51	25	3700

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Appendix 9 - 2 Motor Activity      Stage : Week 4      0.5 mg/kg      Male

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
20201		2504	1544	151	11	53	66	4329
20202		2362	1824	401	741	1588	388	7304
20203		1717	2369	1675	1564	50	120	7495
20204		0	2316	1679	404	82	67	4548
20205		1999	2029	236	4	16	6	4290

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Appendix 9 - 3    Motor Activity                          Stage : Week 4    5 mg/kg                          Male

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
20301		2429	1631	398	0	42	133	4633
20302		1969	1646	42	0	0	2	3659
20303		1695	1705	296	1	29	8	3734
20304		2335	1232	110	2	95	24	3798
20305		1825	1728	1562	2504	999	233	8851

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Appendix 9 - 4      Motor Activity      Stage : Week 4      50 mg/kg      Male

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
20401		2400	1867	1682	1734	378	0	8061
20402		2339	1892	1543	2008	1921	1267	10970
20403		2414	1667	246	0	14	10	4351
20404		2058	2126	1469	1263	1129	246	8291
20405		1876	2152	1839	851	4	23	6745
20406		2196	1926	1068	169	0	2	5361
20407		2155	1886	1316	354	46	34	5791
20408		2459	1929	2125	1992	1490	56	10051
20409		2345	1912	420	81	59	23	4840
20410		2279	1447	884	94	69	124	4897

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Appendix 9 - 5    Motor Activity                      Stage : Week 4    0 mg/kg                      Female

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
60101		2055	1344	840	2154	1759	455	8607
60102		2162	626	0	6	6	23	2823
60103		2808	1887	2047	319	78	192	7331
60104		2764	1825	2384	1998	2201	1991	13163
60105		2107	2037	2076	1590	1496	395	9701
60106		2367	2201	916	10	51	143	5688
60107		2318	261	0	0	1007	219	3805
60108		2498	2344	1406	367	421	221	7257
60109		2807	1713	1004	31	117	269	5941
60110		2564	2333	1738	1505	156	32	8328

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Appendix 9 - 6 Motor Activity      Stage : Week 4      0.5 mg/kg      Female

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
60201		2056	1723	656	20	2	241	4698
60202		2333	57	22	38	0	62	2512
60203		2639	290	25	0	0	5	2959
60204		2548	2124	504	0	0	108	5284
60205		2633	1561	121	15	16	23	4369

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Appendix 9 - 7      Motor Activity      Stage : Week 4      5 mg/kg      Female

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
60301		2069	1591	1631	1048	0	10	6349
60302		2016	1820	68	0	24	1127	5055
60303		2678	2549	2086	2015	466	308	10102
60304		2476	687	28	4	212	178	3585
60305		2331	1725	13	2	0	0	4071

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Appendix 9 - 8      Motor Activity      Stage : Week 4      50 mg/kg      Female

Animal Number	Time Unit	0-10min count/10min	10-20min count/10min	20-30min count/10min	30-40min count/10min	40-50min count/10min	50-60min count/10min	Total count/hour
60401	2401	1505	374	20	64	28		4392
60402	2006	980	0	4	23	14		3027
60403	2695	2625	1622	2020	1828	2496		13286
60404	2633	1152	7	57	128	35		4012
60405	2275	2015	2286	517	109	1400		8602
60406	1764	1911	1538	1118	5	8		6344
60407	2407	2406	561	0	15	7		5396
60408	2633	1938	2153	1211	187	486		8608
60409	2495	2366	1936	2003	370	302		9472
60410	2938	2372	1554	415	63	226		7568

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Appendix 10 - 1		Body Weight		C B I		0 mg/kg		Male		Unit : g
Animal Number	Day	1	8	15	22	28	29	36	42	
20101		161	216	265	317	351	FB			
20102		154	197	240	286	318	FB			
20103		158	228	286	340	388	FB			
20104		159	224	281	340	381	FB			
20105		153	211	273	323	358	FB			
20106		165	224	285	346	385	381	415	448	
20107		152	211	266	320	362	356	409	432	
20108		161	217	268	311	342	336	371	399	
20109		160	217	275	327	362	350	402	427	
20110		156	218	272	331	378	377	415	444	

FB , Fasted body weight

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Appendix 10 - 2    Body Weight		C B I		0.5 mg/kg		Male	Unit : g
Animal Number	Day	1	8	15	22	28	29
20201		167	233	290	355	389	FB
20202		161	213	262	306	341	FB
20203		157	221	283	354	400	FB
20204		149	202	256	301	331	FB
20205		150	214	280	336	375	FB

FB , Fasted body weight

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Appendix 10 - 3		Body Weight		C B I		5 mg/kg	Male	Unit : g
Animal Number	Day	1	8	15	22	28	29	
20301		157	213	263	319	358	FB	
20302		150	210	263	318	355	FB	
20303		151	207	254	291	321	FB	
20304		163	219	274	323	362	FB	
20305		166	243	309	368	409	FB	

FB , Fasted body weight

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Appendix 10 - 4		Body Weight		C B I		50 mg/kg		Male		Unit : g
Animal Number	Day	1	8	15	22	28	29	36	42	
20401		155	202	224	257	262	FB			
20402		152	201	247	291	314	FB			
20403		154	199	227	251	271	FB			
20404		161	209	250	268	280	FB			
20405		160	221	265	317	350	FB			
20406		168	225	268	301	307	307	346	385	
20407		146	207	267	313	345	347	395	435	
20408		161	182	228	275	301	294	357	393	
20409		153	202	240	282	306	301	337	370	
20410		159	210	259	314	350	349	383	418	

FB , Fasted body weight

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Appendix 10 - 5		Body Weight		CB		0 mg/kg		Female		Unit : g
Animal Number	Day	1	8	15	22	28	29	36	42	
60101		129	159	181	206	213	FB			
60102		122	159	187	213	234	FB			
60103		142	193	217	242	265	FB			
60104		138	175	192	213	237	FB			
60105		144	170	203	228	239	FB			
60106		137	176	205	233	260	257	280	294	
60107		139	173	197	223	233	244	249	272	
60108		133	159	184	192	221	216	230	233	
60109		143	183	202	217	244	244	257	277	
60110		137	168	184	207	226	226	246	254	

FB , Fasted body weight

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Appendix 10 - 6		Body Weight		C B I		0.5 mg/kg	Female	Unit : g
Animal Number	Day	1	8	15	22	28	29	
60201	128	155	178	201	213	FB		
60202	143	186	214	248	273	FB		
60203	142	169	185	211	229	FB		
60204	128	173	202	229	253	FB		
60205	135	157	180	193	207	FB		

FB , Fasted body weight

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Appendix 10 - 7 Body Weight		C B I		5 mg/kg		Female	Unit : g
Animal Number	Day	1	8	15	22	28	29
60301		127	165	187	212	230	FB
60302		140	169	185	208	227	FB
60303		132	167	194	221	234	FB
60304		133	161	173	199	216	FB
60305		145	177	211	240	257	FB

FB , Fasted body weight

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Appendix 10 - 8 Body Weight		C B I		50 mg/kg		Female		Unit : g	
Animal Number	Day	1	8	15	22	28	29	36	42
60401	139	176	187	206	221	FB			
60402	134	173	189	216	231	FB			
60403	128	157	183	207	216	FB			
60404	145	184	204	232	243	FB			
60405	140	175	191	217	232	FB			
60406	140	172	193	216	233	231	254	269	
60407	136	167	196	222	233	238	247	271	
60408	132	163	178	183	209	200	223	216	
60409	134	156	182	193	207	212	223	237	
60410	140	170	199	225	233	242	245	269	

FB , Fasted body weight

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Appendix 11 - 1 Food Consumption		C B I		0 mg/kg		Male		Unit : g/animal/day
Animal Number	Day	8	15	22	26	36	40	
20101		25.1	25.9	28.1	28.3			
20102		23.0	24.1	26.0	27.0			
20103		26.6	30.4	31.0	32.3			
20104		26.1	28.1	31.9	31.3			
20105		24.7	28.9	30.7	30.3			
20106		26.9	30.6	34.1	33.5	31.4	33.8	
20107		25.6	28.6	30.9	30.0	32.3	31.5	
20108		25.9	29.1	30.4	29.0	28.9	30.0	
20109		25.6	29.6	32.6	31.0	31.7	32.8	
20110		25.9	28.0	32.3	30.3	33.7	33.0	

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Appendix 11 - 2 Food Consumption						CB	0.5 mg/kg	Male	Unit : g/animal/day
Animal Number	Day	8	15	22	26				
20201		27.9	30.0	33.6	33.0				
20202		23.6	26.1	29.0	29.0				
20203		25.4	28.7	30.4	30.8				
20204		22.9	25.6	27.6	28.3				
20205		26.1	30.1	31.9	29.8				

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Appendix 11 - 3 Food Consumption		CBI		5 mg/kg	Male	Unit : g/animal/day
Animal Number	Day	8	15	22	26	
20301		24.4	27.6	32.7	31.3	
20302		25.4	27.4	35.6	37.3	
20303		23.9	28.1	30.3	29.8	
20304		26.3	32.1	35.3	36.0	
20305		29.4	33.1	37.7	37.0	

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Appendix 11 - 4 Food Consumption		C B I		50 mg/kg	Male	Unit : g/animal/day	
Animal Number	Day	8	15	22	26	36	40
20401		20.9	23.3	25.9	21.5		
20402		24.0	31.0	34.3	32.8		
20403		21.4	24.3	25.9	28.0		
20404		25.1	32.6	29.4	24.0		
20405		26.1	31.9	34.7	34.0		
20406		25.4	29.7	31.6	27.5	29.4	28.5
20407		23.7	31.3	33.1	33.0	33.3	33.5
20408		21.4	27.4	29.3	27.0	37.0	34.3
20409		23.0	28.3	29.6	28.5	28.6	30.0
20410		23.3	31.9	34.9	34.8	32.0	29.0

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Appendix 11 - 5 Food Consumption

C B | 0 mg/kg

Female

Unit : g/animal/day

Animal Number	Day	8	15	22	26	36	40
60101		19.7	20.3	21.1	20.8		
60102		18.4	21.0	22.6	20.3		
60103		23.6	22.4	23.9	23.5		
60104		19.3	19.4	20.9	19.8		
60105		20.9	24.4	24.7	23.3		
60106		20.0	22.3	22.3	24.0	25.4	24.0
60107		21.4	22.0	23.3	22.5	24.3	25.0
60108		18.9	19.7	20.7	20.5	21.0	20.5
60109		20.6	20.9	21.0	22.8	23.0	23.8
60110		19.1	20.3	22.6	21.0	22.7	22.3

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Appendix 11 - 6 Food Consumption		C B I		0.5 mg/kg	Female	Unit : g/animal/day
Animal Number	Day	8	15	22	26	
60201		16.9	18.0	19.3	19.3	
60202		22.3	24.3	26.6	25.8	
60203		19.6	20.0	22.4	21.5	
60204		19.4	21.1	23.0	23.3	
60205		17.4	18.9	18.1	19.0	

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Appendix 11 - 7 Food Consumption		C B I		5 mg/kg	Female	Unit : g/animal/day
Animal Number	Day	8	15	22	26	
60301		19.4	21.1	21.9	21.3	
60302		18.6	19.7	21.4	21.5	
60303		19.3	20.3	22.6	20.8	
60304		17.9	19.6	21.9	20.8	
60305		19.9	23.0	24.0	22.8	

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Appendix 11 - 8 Food Consumption		C B		50 mg/kg	Female		Unit : g/animal/day
Animal Number	Day	8	15	22	26	36	40
60401		20.3	18.4	20.9	20.3		
60402		19.7	19.9	21.1	20.0		
60403		19.0	20.7	21.4	22.0		
60404		19.9	20.3	22.1	20.3		
60405		20.0	20.0	22.1	21.8		
60406		18.9	19.6	21.3	21.5	24.9	23.0
60407		18.4	20.0	20.4	19.3	21.6	22.3
60408		18.4	18.9	19.6	18.8	20.9	19.5
60409		17.6	20.3	20.3	19.8	21.0	20.8
60410		19.9	21.6	22.7	21.8	24.0	23.0

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Appendix 12 - 1 Hematology

C B I 0 mg/kg

Male

Animal Number	Red Blood Cell Count		Hemoglobin		Hematocrit		MCV		MCH			
	x10 <sup>6</sup> /µL	Day 29	g/dL	Day 29	Day 43	%	Day 29	Day 43	fL	pg	Day 29	Day 43
20101	8.54			16.7		47.4			55.5		19.6	
20102	7.95			15.7		44.7			56.2		19.7	
20103	7.88			15.8		46.3			58.8		20.1	
20104	8.55			16.4		46.4			54.3		19.2	
20105	8.12			16.0		45.0			55.4		19.7	
20106		8.37		16.5		46.5			55.6		19.7	
20107		8.36		16.2		45.3			54.2		19.4	
20108		8.39		16.8		47.1			56.1		20.0	
20109		8.37		15.1		42.7			51.0		18.0	
20110		7.94		15.3		43.1			54.3		19.3	

Animal Number	MCHC		Platelet Count		Reticulocyte Ratio		PT		APTT				
	g/dL	Day 29	Day 43	x10 <sup>3</sup> /µL	Day 29	Day 43	%	sec	Day 29	Day 43	sec	Day 29	Day 43
20101	35.2			997		3.61			20.8			23.2	
20102	35.1			1110		4.09			17.2			18.3	
20103	34.1			1151		4.31			26.0			22.4	
20104	35.3			1271		4.46			26.7			24.5	
20105	35.6			1254		3.97			19.2			21.4	
20106		35.5		1229		3.83			20.9			21.0	
20107		35.8		1228		3.21			17.8			20.3	
20108		35.7		1186		3.83			20.9			21.5	
20109		35.4		1253		4.71			17.0			18.7	
20110		35.5		1230		5.05			17.3			17.7	

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Appendix 12 - 1 Hematology

C B I

0 mg/kg

Male

Animal Number	White Blood Cell Count $\times 10^3/\mu\text{L}$		Lymphocyte %		Neutrophil %		Eosinophil %		Basophil %	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
20101	8.66		74.5		21.7		0.8		0.0	
20102	8.94		83.6		12.9		1.1		0.1	
20103	10.27		79.5		17.1		0.8		0.0	
20104	9.27		82.5		13.5		1.5		0.0	
20105	14.65		83.9		12.8		0.5		0.1	
20106		5.55		72.3		22.4		1.3		0.0
20107		12.52		83.3		12.1		1.4		0.1
20108		10.15		84.0		12.3		0.4		0.0
20109		14.20		81.5		13.0		0.8		0.1
20110		10.84		77.1		17.8		0.9		0.0

Monocyte

Animal Number	% Day 29	Day 43
20101	3.0	
20102	2.3	
20103	2.6	
20104	2.5	
20105	2.7	
20106		4.0
20107		3.1
20108		3.3
20109		4.6
20110		4.2

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Appendix 12 - 2 Hematology

C E I 0.5 mg/kg

Male

Animal Number	Red Blood Cell Count	Hemoglobin conc.	Hematocrit	MCV	MCH	MCHC	Platelet Count	Reticulocyte Ratio	PT	APTT
	x10 <sup>6</sup> /µL Day 29	g/dL Day 29	% Day 29	fL Day 29	pg Day 29	g/dL Day 29	x10 <sup>3</sup> /µL Day 29	% Day 29	sec Day 29	sec Day 29
20201	7.40	14.8	42.4	57.3	20.0	34.9	1373	4.77	24.3	22.0
20202	8.09	15.3	44.5	55.0	18.9	34.4	1317	3.40	36.8	23.3
20203	7.05	13.7	40.6	57.6	19.4	33.7	1297	5.76	17.1	19.7
20204	7.66	15.7	44.9	58.6	20.5	35.0	980	6.59	21.1	20.1
20205	6.79	14.2	41.1	60.5	20.9	34.5	1054	5.98	24.7	24.5

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Appendix 12 - 2 Hematology

CB 0.5 mg/kg

Male

Animal Number	White Blood Cell Count	Lymphocyte	Neutrophil	Eosinophil	Basophil	Monocyte
	x10 <sup>3</sup> /µL Day 29	% Day 29	% Day 29	% Day 29	% Day 29	% Day 29
20201	10.59	84.0	13.0	1.3	0.1	1.6
20202	14.32	82.4	13.3	0.7	0.0	3.6
20203	9.00	76.9	18.5	0.8	0.0	3.8
20204	14.11	85.1	11.1	1.0	0.0	2.8
20205	10.80	76.1	18.4	1.0	0.1	4.4

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Appendix 12 - 3 Hematology

C B I

5 mg/kg

Male

Animal Number	Red Blood Cell Count	Hemoglobin conc.	Hematocrit	MCV	MCH	MCHC	Platelet Count	Reticulocyte Ratio	PT	APTT
	x10 <sup>6</sup> /µL Day 29	g/dL Day 29	% Day 29	fL Day 29	pg Day 29	g/dL Day 29	x10 <sup>3</sup> /µL Day 29	% Day 29	sec Day 29	sec Day 29
20301	6.33	13.2	39.5	62.4	20.9	33.4	1306	6.66	24.4	22.7
20302	7.58	14.8	43.4	57.3	19.5	34.1	1198	4.28	20.4	22.7
20303	7.61	15.0	43.2	56.8	19.7	34.7	1166	4.59	24.8	23.3
20304	7.77	15.1	43.4	55.9	19.4	34.8	1149	5.28	31.5	23.9
20305	6.88	13.8	40.6	59.0	20.1	34.0	1274	6.25	20.9	21.2

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Appendix 12 - 3 Hematology

C B I

5 mg/kg

Male

Animal Number	White Blood Cell Count	Lymphocyte	Neutrophil	Eosinophil	Basophil	Monocyte
	x10 <sup>3</sup> /µL	%	%	%	%	%
	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29
20301	16.67	82.9	14.0	0.7	0.1	2.3
20302	8.91	79.5	15.5	0.7	0.0	4.3
20303	16.07	77.7	19.4	0.7	0.1	2.1
20304	11.85	87.8	9.1	1.1	0.1	1.9
20305	9.95	83.1	12.8	0.8	0.1	3.2

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Appendix 12 - 4 Hematology

C B I

50 mg/kg

Male

Animal Number	Red Blood Cell Count x10 <sup>6</sup> /µL		Hemoglobin conc. g/dL		Hematocrit %		MCV fL		MCH pg	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
20401	6.77		12.4		36.6		54.1		18.3	
20402	7.20		13.1		39.3		54.6		18.2	
20403	7.52		14.1		41.0		54.5		18.8	
20404	7.26		12.8		37.6		51.8		17.6	
20405	7.61		14.3		41.8		54.9		18.8	
20406		7.27		13.3		39.4		54.2		18.3
20407		7.57		14.5		41.8		55.2		19.2
20408		6.64		13.3		39.7		59.8		20.0
20409		8.15		14.4		41.8		51.3		17.7
20410		7.91		14.8		42.7		54.0		18.7
MCHC		Platelet Count x10 <sup>3</sup> /µL		Reticulocyte Ratio %		PT sec		APTT sec		
Animal Number	g/dL	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	
20401	33.9		1450		4.58		19.5		18.9	
20402	33.3		1304		4.64		28.1		24.7	
20403	34.4		1608		4.02		23.0		24.4	
20404	34.0		1345		4.88		28.2		22.9	
20405	34.2		1567		4.47		22.0		20.1	
20406		33.8		1120		6.85		16.3		18.3
20407		34.7		1229		6.42		19.0		24.8
20408		33.5		1515		7.80		19.3		21.6
20409		34.4		1242		4.68		26.4		21.2
20410		34.7		1331		6.41		24.8		23.0

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Appendix 12 - 4 Hematology

C B I

50 mg/kg

Male

Animal Number	White Blood Cell Count		Lymphocyte		Neutrophil		Eosinophil		Basophil	
	x10 <sup>3</sup> /µL	%	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
20401	10.58		77.0		19.7		1.2		0.0	
20402	9.23		83.1		12.5		0.5		0.1	
20403	17.76		72.0		25.2		0.6		0.1	
20404	15.57		81.4		15.3		0.6		0.1	
20405	14.31		73.3		20.0		2.4		0.0	
20406		11.92		82.6		13.3		0.9		0.0
20407		10.71		79.6		15.1		1.6		0.0
20408		11.44		79.6		16.9		0.5		0.0
20409		13.85		80.8		16.0		0.6		0.0
20410		11.16		75.5		18.0		1.0		0.0

Monocyte

Animal Number	%	Day 29	Day 43
20401		2.1	
20402		3.8	
20403		2.1	
20404		2.6	
20405		4.3	
20406		3.2	
20407		3.7	
20408		3.0	
20409		2.6	
20410		5.5	

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Appendix 12 - 5 Hematology

[ C B I ] 0 mg/kg

Female

Animal Number	Red Blood Cell Count		Hemoglobin conc.		Hematocrit		MCV		MCH			
	x10 <sup>6</sup> /µL	Day 29	g/dL	Day 29	Day 43	%	Day 29	Day 43	fL	pg	Day 29	Day 43
60101	8.38		16.4			45.6			54.4		19.6	
60102	7.25		14.9			42.3			58.3		20.6	
60103	7.85		16.2			45.1			57.5		20.6	
60104	7.62		15.1			42.4			55.6		19.8	
60105	8.02		15.8			44.6			55.6		19.7	
60106		8.82		16.4			45.1			51.1		18.6
60107		7.80		14.8			41.3			52.9		19.0
60108		8.47		16.1			44.7			52.8		19.0
60109		8.08		15.5			43.3			53.6		19.2
60110		7.97		15.4			43.4			54.5		19.3
MCHC		Platelet Count		Reticulocyte Ratio		PT		APTT				
Animal Number	g/dL	Day 29	Day 43	x10 <sup>3</sup> /µL	Day 29	Day 43	%	sec	Day 29	Day 43	sec	
60101	36.0		1261		2.52			Day 29	16.9		16.1	
60102	35.2		1040		3.44			Day 43	17.7		15.0	
60103	35.9		1218		2.72			Day 29	16.9		16.0	
60104	35.6		1185		3.86			Day 43	16.9		14.6	
60105	35.4		1309		4.02			Day 29	17.0		14.6	
60106		36.4		1040		2.82			17.2		16.5	
60107		35.8		1050		3.89			17.8		16.4	
60108		36.0		1177		2.82			16.9		14.1	
60109		35.8		1260		4.29			17.2		16.1	
60110		35.5		1107		4.82			16.3		16.4	

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Appendix 12 - 5 Hematology

C B I 0 mg/kg

Female

Animal Number	White Blood Cell Count		Lymphocyte		Neutrophil		Eosinophil		Basophil	
	x10 <sup>3</sup> /µL	%	Day 29	Day 43	%	Day 29	Day 43	%	Day 29	Day 43
60101	8.21		89.8		7.7		0.7		0.0	
60102	7.31		85.6		9.6		0.8		0.0	
60103	11.54		86.6		8.9		1.6		0.1	
60104	6.94		78.5		19.1		1.0		0.0	
60105	6.90		86.4		9.7		1.9		0.0	
60106		5.34		85.4		10.1		1.7		0.0
60107		6.09		75.5		20.3		0.8		0.0
60108		7.73		75.8		18.4		1.0		0.0
60109		11.16		74.6		22.8		0.9		0.0
60110		12.21		79.0		15.8		1.6		0.1

Monocyte

Animal Number	%	Day 29	Day 43
60101		1.8	
60102		4.0	
60103		2.8	
60104		1.4	
60105		2.0	
60106		2.8	
60107		3.4	
60108		4.8	
60109		1.7	
60110		3.5	

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Appendix 12 - 6 Hematology

C B I

0.5 mg/kg

Female

Animal Number	Red Blood Cell Count	Hemoglobin conc.	Hematocrit	MCV	MCH	MCHC	Platelet Count	Reticulocyte Ratio	PT	APTT
	x10 <sup>6</sup> /µL Day 29	g/dL Day 29	% Day 29	fL Day 29	pg Day 29	g/dL Day 29	x10 <sup>3</sup> /µL Day 29	% Day 29	sec Day 29	sec Day 29
60201	7.91	15.5	42.9	54.2	19.6	36.1	1135	3.27	17.5	16.1
60202	8.26	16.0	44.5	53.9	19.4	36.0	1044	3.31	16.6	15.9
60203	7.53	15.1	42.3	56.2	20.1	35.7	989	3.43	18.2	15.9
60204	7.64	15.0	42.5	55.6	19.6	35.3	1170	3.74	16.5	13.9
60205	8.07	16.2	45.1	55.9	20.1	35.9	1072	2.80	16.9	15.3

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Appendix 12 - 6 Hematology      **C B I**      0.5 mg/kg      Female

Animal Number	White Blood Cell Count	Lymphocyte	Neutrophil	Eosinophil	Basophil	Monocyte
	x10 <sup>3</sup> /µL	%	%	%	%	%
	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29
60201	6.95	88.6	7.8	1.3	0.0	2.3
60202	7.72	83.7	10.6	0.6	0.0	5.1
60203	10.18	87.8	9.3	0.8	0.0	2.1
60204	7.38	77.4	16.7	1.4	0.0	4.5
60205	11.66	86.8	9.6	0.9	0.0	2.7

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Appendix 12 - 7 Hematology

CB I

5 mg/kg

Female

Animal Number	Red Blood Cell Count	Hemoglobin conc.	Hematocrit	MCV	MCH	MCHC	Platelet Count	Reticulocyte Ratio	PT	APTT
	x10 <sup>6</sup> /µL	g/dL	%	fL	pg	g/dL	x10 <sup>3</sup> /µL	%	sec	sec
	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29
60301	7.26	14.4	40.2	55.4	19.8	35.8	1209	3.82	17.1	14.5
60302	7.51	15.0	41.7	55.5	20.0	36.0	1120	3.29	16.9	15.2
60303	7.42	15.0	43.1	58.1	20.2	34.8	952	3.67	16.9	15.0
60304	8.30	16.3	45.0	54.2	19.6	36.2	1428	2.68	18.0	15.5
60305	7.99	15.6	43.8	54.8	19.5	35.6	994	3.10	17.0	15.8

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Appendix 12 - 7 Hematology      **C B** 5 mg/kg      Female

Animal Number	White Blood Cell Count	Lymphocyte	Neutrophil	Eosinophil	Basophil	Monocyte
	x10 <sup>3</sup> /µL Day 29	% Day 29				
60301	7.64	84.6	12.0	1.2	0.0	2.2
60302	10.15	72.2	22.5	1.3	0.1	3.9
60303	9.54	92.3	4.8	0.8	0.1	2.0
60304	13.19	76.0	20.7	0.8	0.1	2.4
60305	8.01	86.9	8.3	1.9	0.0	2.9

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Appendix 12 - 8 Hematology

CB 50 mg/kg

Female

Animal Number	Red Blood Cell Count		Hemoglobin conc.		Hematocrit		MCV		MCH			
	x10 <sup>6</sup> /µL	Day 29	g/dL	Day 29	Day 43	%	Day 29	Day 43	fL	pg	Day 29	Day 43
60401	7.17		14.0			39.7			55.4		19.5	
60402	6.95		13.9			39.7			57.1		20.0	
60403	7.05		14.5			41.8			59.3		20.6	
60404	7.30		14.7			42.3			57.9		20.1	
60405	7.57		15.1			43.2			57.1		19.9	
60406		7.94		14.8			41.9			52.8		18.6
60407		7.91		14.7			41.6			52.6		18.6
60408		7.66		15.2			43.7			57.0		19.8
60409		8.04		15.0			41.5			51.6		18.7
60410		7.59		14.8			42.4			55.9		19.5
<hr/>												
Animal Number	MCHC		Platelet Count		Reticulocyte Ratio		PT		APTT			
	g/dL	Day 29	Day 43	x10 <sup>3</sup> /µL	Day 29	Day 43	%	sec	Day 29	Day 43	sec	
60401	35.3		957		2.97			15.8			17.1	
60402	35.0		1161		3.70			14.9			18.5	
60403	34.7		987		3.19			15.7			16.3	
60404	34.8		1113		2.39			15.6			18.1	
60405	35.0		1179		2.84			16.0			20.0	
60406		35.3		996			3.39		16.3		17.2	
60407		35.3		1265			3.50		16.2		18.6	
60408		34.8		1081			2.42		16.3		17.2	
60409		36.1		940			2.99		16.3		17.8	
60410		34.9		1032			4.34		16.2		16.7	

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Appendix 12 - 8 Hematology

C B I

50 mg/kg

Female

Animal Number	White Blood Cell Count x10 <sup>3</sup> /µL		Lymphocyte %		Neutrophil %		Eosinophil %		Basophil %	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
60401	8.58		83.8		12.5		0.8		0.0	
60402	6.62		86.6		9.9		1.1		0.0	
60403	15.43		93.8		3.8		0.3		0.1	
60404	9.61		90.8		6.3		0.4		0.0	
60405	16.79		91.1		6.4		0.4		0.0	
60406		6.22		92.1		5.4		0.6		0.0
60407		7.05		80.1		16.2		1.1		0.0
60408		9.14		76.7		18.7		0.9		0.1
60409		5.18		79.2		16.0		0.6		0.0
60410		5.74		93.0		4.2		0.7		0.0
Monocyte										
Animal Number	%									
60401	2.9									
60402	2.4									
60403	2.0									
60404	2.5									
60405	2.1									
60406		1.9								
60407		2.6								
60408		3.6								
60409		4.2								
60410		2.1								

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Appendix 13 - 1 Blood Chemistry

C B I

0 mg/kg

Male

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin mg/dL	
	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	Day 29	Day 43
20101	77		19		1		674		0.0	
20102	111		28		1		739		0.0	
20103	91		23		1		738		0.0	
20104	77		18		1		660		0.0	
20105	82		21		1		550		0.0	
20106		114		26		1		600		0.0
20107		85		26		1		425		0.0
20108		88		24		1		556		0.0
20109		126		30		1		590		0.1
20110		104		25		1		522		0.1
Animal Number	Urea Nitrogen mg/dL		Creatinine mg/dL		Glucose mg/dL		Total Cholesterol mg/dL		Triglyceride mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
20101	13.4		0.2		136		55		34	
20102	13.5		0.2		133		80		25	
20103	9.3		0.2		125		50		28	
20104	13.2		0.2		123		71		37	
20105	11.2		0.2		124		86		44	
20106		12.0		0.2		126		62		49
20107		9.5		0.2		110		59		25
20108		13.5		0.3		120		78		22
20109		11.7		0.2		124		73		43
20110		15.9		0.2		117		76		23

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Appendix 13 - 1 Blood Chemistry

C B

0 mg/kg

Male

Animal Number	Total Protein g/dL		Albumin g/dL		A/G Ratio		Calcium mg/dL		Inorganic Phosphorus mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
20101	6.2		3.2		1.08		10.4		8.6	
20102	6.4		3.1		0.97		10.0		8.9	
20103	6.4		3.1		0.94		10.2		9.2	
20104	6.6		3.0		0.86		10.6		9.8	
20105	6.7		3.1		0.85		10.1		9.1	
20106		6.5		3.0		0.83		9.8		9.0
20107		6.6		3.1		0.90		10.2		8.3
20108		6.5		3.0		0.84		9.9		9.1
20109		6.7		3.1		0.86		10.1		8.8
20110		6.5		3.1		0.91		10.2		9.0
Animal Number	Na mmol/L		K mmol/L		Cl mmol/L					
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43				
20101	147		3.9		102					
20102	147		4.3		104					
20103	147		4.6		103					
20104	148		4.1		104					
20105	146		4.5		103					
20106		147		4.5		105				
20107		146		4.1		102				
20108		148		4.5		106				
20109		144		4.6		101				
20110		146		4.6		103				

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Appendix 13 - 2 Blood Chemistry      **C B I**      0.5 mg/kg      Male

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin	Urea Nitrogen	Creatinine	Glucose	Total Cholesterol	Triglyceride	Total Protein
	U/L	Day 29	U/L	Day 29	U/L	Day 29	U/L	Day 29	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	g/dL
20201	104		31		1		515		0.0	14.4	0.2	137	38	26	6.8
20202	88		26		1		1121		0.0	16.8	0.2	163	29	26	6.3
20203	76		21		1		830		0.0	13.4	0.2	146	76	23	6.3
20204	89		31		1		985		0.1	21.3	0.2	146	66	36	6.2
20205	85		23		0		978		0.0	16.4	0.2	141	58	36	6.2

Animal Number	Albumin	A/G Ratio	Calcium	Inorganic Phosphorus	Na	K	Cl
	g/dL	Day 29	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L
20201	3.6	1.10	10.1	9.5	148	4.4	105
20202	3.6	1.32	10.0	9.7	147	4.3	105
20203	3.4	1.17	9.6	9.0	145	4.3	105
20204	3.4	1.21	9.9	10.8	147	4.4	103
20205	3.4	1.19	10.1	9.7	147	4.5	106

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Appendix 13 - 3 Blood Chemistry

C B | 5 mg/kg

Male

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin	Urea Nitrogen	Creatinine	Glucose	Total Cholesterol	Triglyceride	Total Protein
	U/L	Day 29	U/L	Day 29	U/L	Day 29	U/L	Day 29	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	g/dL
20301	100	27		1	1138		0.1	14.9		0.2	131		42	24	6.9
20302	97	38		0	1246		0.0	17.3		0.2	135		36	22	6.7
20303	88	32		1	1361		0.1	17.8		0.2	159		62	31	6.9
20304	106	30		1	918		0.1	18.4		0.1	153		54	26	7.1
20305	92	23		1	731		0.1	14.2		0.2	158		78	23	7.0

Animal Number	Albumin	A/G Ratio	Calcium	Inorganic Phosphorus	Na	K	Cl
	g/dL		mg/dL	mg/dL	mmol/L	mmol/L	mmol/L
20301	3.8	1.21	10.3	9.5	145	5.0	104
20302	3.7	1.25	10.2	10.7	145	4.7	105
20303	3.9	1.35	10.4	9.4	146	4.2	102
20304	3.9	1.19	10.3	10.7	148	4.5	102
20305	3.8	1.21	10.4	9.7	143	4.9	102

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Appendix 13 - 4 Blood Chemistry

C B I

50 mg/kg

Male

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin mg/dL	
	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	Day 29	Day 43
20401	109		26		1		1119		0.1	
20402	191		92		1		1318		0.1	
20403	74		35		1		1317		0.1	
20404	123		42		0		1232		0.1	
20405	99		33		1		1039		0.1	
20406		93		41		1		624		0.0
20407		118		42		1		452		0.0
20408		71		23		0		535		0.0
20409		79		32		0		632		0.0
20410		80		47		0		483		0.0

Animal Number	Urea Nitrogen mg/dL		Creatinine mg/dL		Glucose mg/dL		Total Cholesterol mg/dL		Triglyceride mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
20401	16.0		0.1		146		114		14	
20402	17.6		0.2		161		57		20	
20403	17.2		0.2		152		72		25	
20404	19.1		0.2		154		41		21	
20405	19.7		0.2		145		110		31	
20406		10.5		0.2		122		154		48
20407		9.8		0.2		110		111		28
20408		13.1		0.2		147		130		37
20409		10.1		0.2		148		101		27
20410		10.9		0.2		122		120		21

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Appendix 13 - 4 Blood Chemistry

C B I

50 mg/kg

Male

Animal Number	Total Protein g/dL		Albumin g/dL		A/G Ratio		Calcium mg/dL		Inorganic Phosphorus mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
20401	6.3		3.5		1.26		9.9		8.8	
20402	6.6		3.7		1.24		9.7		9.7	
20403	6.7		4.1		1.55		10.4		9.2	
20404	6.2		3.4		1.20		9.7		9.9	
20405	6.8		3.9		1.32		10.5		9.4	
20406		7.7		3.9		1.03		11.0		9.3
20407		7.6		3.7		0.92		10.6		8.8
20408		7.3		3.7		1.06		10.2		9.4
20409		7.0		3.6		1.05		10.5		9.1
20410		7.2		3.5		0.95		10.7		9.1
Animal Number	Na mmol/L		K mmol/L		Cl mmol/L					
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43				
20401	147		4.5		107					
20402	146		4.8		105					
20403	146		4.1		104					
20404	146		4.3		106					
20405	145		4.7		104					
20406		145		4.5		102				
20407		144		4.7		100				
20408		145		4.3		103				
20409		145		4.5		104				
20410		146		4.2		101				

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Appendix 13 - 5 Blood Chemistry

C B I

0 mg/kg

Female

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin mg/dL	
	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	Day 29	Day 43
60101	81		19		1		301		0.0	
60102	88		17		1		287		0.1	
60103	80		15		1		437		0.0	
60104	87		13		1		366		0.0	
60105	96		17		1		226		0.0	
60106		78		19		0		202		0.0
60107		99		19		1		205		0.0
60108		98		18		1		175		0.1
60109		100		18		1		302		0.1
60110		80		20		1		292		0.0
Animal Number	Urea Nitrogen mg/dL		Creatinine mg/dL		Glucose mg/dL		Total Cholesterol mg/dL		Triglyceride mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
60101	12.1		0.2		116		71		12	
60102	13.9		0.2		121		102		11	
60103	8.1		0.2		125		78		19	
60104	10.7		0.2		117		98		7	
60105	13.7		0.2		106		93		12	
60106		13.4		0.2		125		97		27
60107		11.5		0.2		127		103		10
60108		13.2		0.2		93		75		14
60109		14.0		0.3		129		94		14
60110		17.8		0.3		117		84		16

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Appendix 13 - 5 Blood Chemistry

C B I

0 mg/kg

Female

Animal Number	Total Protein g/dL		Albumin g/dL		A/G Ratio		Calcium mg/dL		Inorganic Phosphorus mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
60101	6.3		3.1		0.95		10.1		8.1	
60102	6.8		3.5		1.05		10.5		8.7	
60103	6.1		2.9		0.89		10.5		8.9	
60104	6.6		3.3		1.00		10.1		7.9	
60105	6.6		3.3		1.00		10.3		8.1	
60106		7.5		3.8		1.05		11.6		7.4
60107		6.9		3.5		1.01		9.9		6.9
60108		6.4		3.1		0.94		9.9		7.1
60109		6.9		3.3		0.90		9.6		7.3
60110		6.7		3.0		0.82		9.8		7.3
<hr/>										
Na			K			Cl				
Animal Number	mmol/L	Day 29	Day 43	mmol/L	Day 29	Day 43	mmol/L	Day 29	Day 43	
60101	146			4.0			104			
60102	145			3.9			104			
60103	144			4.5			103			
60104	146			4.0			105			
60105	144			4.4			102			
60106		145			3.9		103			
60107		145			4.0		104			
60108		146			4.3		105			
60109		145			3.8		103			
60110		144			3.9		103			

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Appendix 13 - 6 Blood Chemistry

C B I 0.5 mg/kg

Female

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin	Urea Nitrogen	Creatinine	Glucose	Total Cholesterol	Triglyceride	Total Protein
	U/L	Day 29	U/L	Day 29	U/L	Day 29	U/L	Day 29	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	g/dL
60201	92	17		1	328		0.0	12.4	0.2	104	87	10	87	10	6.5
60202	75	15		1	371		0.0	12.2	0.2	138	99	38	99	38	6.7
60203	86	17		1	304		0.0	11.5	0.2	99	69	9	69	9	6.2
60204	89	18		1	328		0.0	11.3	0.3	102	80	17	102	17	6.6
60205	70	16		1	349		0.0	11.1	0.2	96	54	18	96	18	6.2

Animal Number	Albumin	A/G Ratio	Calcium	Inorganic Phosphorus	Na	K	Cl
	g/dL	Day 29	mg/dL	mg/dL	mmol/L	mmol/L	mmol/L
60201	3.2	0.95	10.3	8.7	145	4.5	104
60202	3.4	1.06	10.8	8.7	145	3.5	103
60203	3.1	0.98	9.6	7.6	143	3.9	104
60204	3.3	1.02	10.7	8.0	145	4.4	104
60205	3.0	0.92	10.2	9.0	148	4.1	105

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Appendix 13 - 7 Blood Chemistry

C B I 5 mg/kg

Female

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin	Urea Nitrogen	Creatinine	Glucose	Total Cholesterol	Triglyceride	Total Protein
	U/L	Day 29	U/L	Day 29	U/L	Day 29	U/L	Day 29	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	mg/dL	g/dL
60301	87	20	1	265		0.0		15.8		0.3		102	70	13	6.4
60302	92	17	1	268		0.0		12.2		0.2		120	73	22	6.6
60303	125	16	1	200		0.0		11.8		0.2		95	74	10	6.7
60304	76	13	0	256		0.0		13.5		0.2		113	92	16	7.2
60305	112	20	1	273		0.0		9.8		0.2		116	71	17	6.5

Animal Number	Albumin	A/G Ratio	Calcium	Inorganic Phosphorus	Na	K	Cl
	g/dL		mg/dL	mg/dL	mmol/L	mmol/L	mmol/L
60301	3.4	1.10	10.2	8.0	146	4.2	106
60302	3.4	1.08	10.3	8.4	146	3.9	104
60303	3.3	0.98	10.1	8.7	145	4.7	105
60304	3.6	1.00	10.5	8.3	145	4.1	102
60305	3.3	1.06	10.5	8.3	146	4.4	104

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Appendix 13 - 8 Blood Chemistry

C B I.

50 mg/kg

Female

Animal Number	ASAT(GOT)		ALAT(GPT)		$\gamma$ GT		ALP		Total Bilirubin mg/dL	
	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	U/L Day 29	Day 43	Day 29	Day 43
60401	69		20		1		148		0.0	
60402	79		18		1		262		0.0	
60403	139		27		0		268		0.0	
60404	111		18		1		289		0.0	
60405	100		24		1		281		0.0	
60406		66		14		0		156		0.0
60407		66		15		1		287		0.0
60408		60		16		0		100		0.0
60409		67		16		1		175		0.0
60410		90		12		1		192		0.0
Animal Number	Urea Nitrogen mg/dL		Creatinine mg/dL		Glucose mg/dL		Total Cholesterol mg/dL		Triglyceride mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
60401	15.2		0.2		116		83		21	
60402	13.4		0.2		125		102		20	
60403	11.0		0.2		119		87		18	
60404	15.8		0.2		122		73		17	
60405	11.1		0.2		111		89		21	
60406		11.9		0.2		126		88		23
60407		11.4		0.2		124		68		17
60408		17.3		0.3		120		72		19
60409		12.8		0.2		121		91		23
60410		14.4		0.2		129		84		30

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Appendix 13 - 8 Blood Chemistry

CB I 50 mg/kg

Female

Animal Number	Total Protein g/dL		Albumin g/dL		A/G Ratio		Calcium mg/dL		Inorganic Phosphorus mg/dL	
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43
60401	7.3		4.0		1.20		10.9		8.7	
60402	7.5		4.1		1.17		10.9		8.0	
60403	7.4		4.0		1.17		10.3		7.5	
60404	7.8		4.3		1.22		10.6		8.6	
60405	7.6		3.9		1.05		10.6		8.3	
60406		7.1		3.5		0.99		10.7		7.7
60407		6.9		3.6		1.09		10.1		7.8
60408		6.9		3.7		1.14		10.4		7.5
60409		7.5		3.9		1.06		10.8		7.6
60410		7.3		3.7		1.04		10.3		7.3
Animal Number	Na mmol/L		K mmol/L		Cl mmol/L					
	Day 29	Day 43	Day 29	Day 43	Day 29	Day 43				
60401	147		4.3		105					
60402	148		4.1		107					
60403	144		4.3		103					
60404	145		4.5		104					
60405	145		4.4		105					
60406		146		3.8		103				
60407		147		3.9		106				
60408		145		3.9		105				
60409		146		4.1		102				
60410		146		3.9		105				

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Appendix 14 - 1 Urinalysis

C B I

0 mg/kg

Male

	pH	Protein	Glucose	Ketones	Occult Blood
Animal Number	Day 26	Day 26	Day 26	Day 26	Day 26
20101	8.5	+/-	-	+/-	-
20102	8.5	+/-	-	+/-	-
20103	8.5	+/-	-	1+	1+
20104	8.5	1+	-	1+	-
20105	8.0	1+	-	1+	-

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## Appendix 14 - 2 Urinalysis

C B I

0.5 mg/kg

Male

Animal Number	pH	Protein	Glucose	Ketones	Occult Blood
	Day 26	Day 26	Day 26	Day 26	Day 26
20201	8.5	1+	-	+/-	-
20202	8.5	+/-	-	+/-	-
20203	8.5	1+	-	1+	-
20204	8.5	+/-	-	+/-	-
20205	8.5	+/-	-	1+	-

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Appendix 14 - 3 Urinalysis

C B I

5 mg/kg

Male

	pH	Protein	Glucose	Ketones	Occult Blood
Animal Number	Day 26	Day 26	Day 26	Day 26	Day 26
20301	8.5	1+	-	1+	-
20302	8.5	1+	-	+/-	-
20303	8.5	1+	-	+/-	-
20304	8.5	-	-	-	+/-
20305	8.5	1+	-	1+	-

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Appendix 14 - 4 Urinalysis

C B I

50 mg/kg

Male

	pH	Protein	Glucose	Ketones	Occult Blood
Animal Number	Day 26	Day 26	Day 26	Day 26	Day 26
20401	8.5	-	-	+/-	-
20402	8.5	-	-	-	-
20403	8.5	+/-	-	-	-
20404	8.5	1+	-	1+	-
20405	8.5	+/-	-	+/-	-

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Appendix 14 - 5 Urinalysis		C B I		0 mg/kg	Female
	pH	Protein	Glucose	Ketones	Occult Blood
Animal Number	Day 26	Day 26	Day 26	Day 26	Day 26
60101	8.0	-	-	-	-
60102	8.5	-	-	+/-	-
60103	8.5	-	-	+/-	-
60104	8.0	1+	-	+/-	-
60105	8.5	-	-	+/-	-

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Appendix 14 - 6 Urinalysis      **C B I**      0.5 mg/kg      Female

	pH	Protein	Glucose	Ketones	Occult Blood
Animal Number	Day 26	Day 26	Day 26	Day 26	Day 26
60201	8.5	1+	-	+/-	-
60202	8.5	1+	-	+/-	-
60203	8.5	1+	-	+/-	-
60204	8.5	-	-	-	-
60205	8.5	-	-	+/-	-

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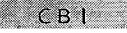
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Appendix 14 - 7 Urinalysis       5 mg/kg      Female

	pH	Protein	Glucose	Ketones	Occult Blood
Animal Number	Day 26	Day 26	Day 26	Day 26	Day 26
60301	8.5	+/-	-	+/-	-
60302	8.5	+/-	-	+/-	-
60303	8.5	1+	-	1+	-
60304	8.5	+/-	-	+/-	-
60305	8.5	+/-	-	-	-

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Appendix 14 - 8 Urinalysis       50 mg/kg      Female

Animal Number	pH	Protein	Glucose	Ketones	Occult Blood
	Day 26	Day 26	Day 26	Day 26	Day 26
60401	8.0	1+	-	1+	-
60402	8.0	-	-	+/-	-
60403	8.5	-	-	-	-
60404	8.5	1+	-	+/-	-
60405	8.5	-	-	-	-

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Appendix 15 - 1 Organ Weight

C B I 0 mg/kg

Male

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart	
	g	Day 29	g	Day 29	mg	Day 29	mg	Day 29	g	Day 29
20101	310		1.93		13.9		519		1.14	
20102	278		2.01		26.0		384		1.06	
20103	351		1.95		28.1		488		1.26	
20104	332		2.16		22.4		744		1.28	
20105	332		2.14		23.0		501		1.24	
20106		415		2.11		31.8		508		1.44
20107		403		2.05		30.0		641		1.26
20108		364		2.01		33.7		646		1.52
20109		388		2.12		31.8		457		1.66
20110		410		2.16		28.3		540		1.46
Liver			Spleen		Kidneys		Adrenals		Testes	
Animal Number	g	Day 29	g	Day 43	g	Day 29	mg	Day 29	g	Day 29
20101	9.10		0.78		2.48		62.8		3.36	
20102	7.76		0.53		2.43		42.2		3.19	
20103	9.88		0.64		2.71		65.0		3.14	
20104	10.06		0.73		2.87		64.1		3.27	
20105	10.09		0.69		2.63		49.6		3.18	
20106		11.40		0.72		3.21		68.1		3.75
20107		11.13		0.62		3.16		63.0		3.42
20108		10.35		0.65		2.57		59.8		2.94
20109		10.96		1.00		3.12		50.5		3.44
20110		11.13		0.72		3.50		48.4		3.70

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Appendix 15 - 1 Organ Weight      CB 0 mg/kg      Male

Epididymides			
Animal Number	g	Day 29	Day 43
20101	0.76		
20102	0.73		
20103	0.84		
20104	0.79		
20105	0.81		
20106		1.23	
20107		1.04	
20108		0.85	
20109		1.05	
20110		1.25	

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Appendix 15 - 2 Organ Weight

CB 1 0.5 mg/kg

Male

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys		Adrenals		Testes		Epididymides	
	g	Day 29	g	Day 29	mg	Day 29	mg	Day 29	g	Day 29	g	Day 29	g	Day 29	g	Day 29	mg	Day 29	g	Day 29	g	Day 29
20201	347		1.94		23.3		764		1.15		16.26		0.71		3.09		60.2		3.08		0.73	
20202	296		1.91		19.4		561		1.04		15.14		0.52		2.41		53.1		3.25		0.73	
20203	360		2.04		25.4		515		1.24		18.06		0.88		3.01		51.1		3.13		0.76	
20204	294		1.97		25.2		548		1.01		17.06		0.68		2.31		49.8		3.24		0.81	
20205	336		2.01		15.7		535		1.11		17.02		0.69		2.66		55.9		3.19		0.73	

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Appendix 15 - 3 Organ Weight      C B I      5 mg/kg      Male

Animal Number	Final Body Weight		Brain	Thyroids	Thymus	Heart	Liver	Spleen	Kidneys	Adrenals	Testes	Epididymides
	g	Day 29	g	mg	Day 29	mg	Day 29	g	Day 29	mg	g	Day 29
20301	320	1.93	30.0	679	1.28	24.48	0.88	3.05	52.5	3.32	0.74	
20302	307	2.05	22.6	448	1.23	23.27	0.62	2.90	45.5	3.62	0.74	
20303	283	1.89	28.3	509	1.10	23.62	0.69	2.32	47.5	3.14	0.75	
20304	320	1.95	27.0	505	1.23	24.77	0.82	3.03	53.1	3.32	0.72	
20305	372	1.99	28.6	572	1.31	28.80	0.88	3.24	52.5	3.20	0.72	

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Appendix 15 - 4 Organ Weight

C B I 50 mg/kg

Male

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart	
	g	Day 29	g	Day 29	mg	Day 29	mg	Day 29	g	Day 29
20401	231		1.93		22.3		326		0.83	
20402	269		1.98		25.0		398		1.09	
20403	243		1.94		36.5		525		0.90	
20404	246		1.82		24.1		327		0.92	
20405	301		1.84		25.6		502		1.17	
20406		349		2.02		24.9		521		1.40
20407		401		2.29		31.8		508		1.50
20408		361		1.96		30.0		698		1.31
20409		338		1.82		33.7		615		1.28
20410		376		1.95		24.8		430		1.40
Liver			Spleen		Kidneys		Adrenals		Testes	
Animal Number	g	Day 29	g	Day 43	g	Day 29	mg	Day 29	g	Day 29
20401	19.06		0.43		2.38		44.1		3.35	
20402	23.18		0.51		2.57		45.6		3.45	
20403	21.51		0.46		2.00		45.1		3.10	
20404	21.30		0.41		2.30		53.2		3.14	
20405	25.13		0.67		2.55		46.7		2.95	
20406		21.13		0.82		2.84		59.1		3.79
20407		18.48		0.89		3.03		69.3		3.64
20408		19.26		0.84		3.01		62.7		4.36
20409		15.88		0.66		2.54		65.3		3.32
20410		19.29		0.76		2.79		61.8		3.42

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Appendix 15 - 4    Organ Weight                          C B I      50 mg/kg      Male

Epididymides			
Animal Number	g	Day 29	Day 43
20401	0.80		
20402	0.74		
20403	0.66		
20404	0.66		
20405	0.72		
20406		1.11	
20407		1.21	
20408		0.97	
20409		1.00	
20410		0.99	

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Appendix 15 - 5 Organ Weight      **C B I**      0 mg/kg      Female

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart		
	g	Day 29	g	Day 29	mg	Day 29	mg	Day 29	g	Day 29	
60101		192		1.94		19.2		625		0.79	
60102		213		1.90		18.2		532		0.90	
60103		238		1.82		21.3		530		0.97	
60104		218		1.94		16.2		560		0.90	
60105		221		1.85		17.2		416		0.82	
60106			265		1.88		18.9		526		0.92
60107			247		1.93		22.3		305		1.00
60108			219		1.90		25.0		451		1.00
60109			250		1.90		23.4		658		0.97
60110			231		1.98		17.0		546		1.03
Liver			Spleen		Kidneys		Adrenals		Ovaries		
Animal Number	g	Day 29	g	Day 43	g	Day 29	mg	Day 29	mg	Day 29	
60101		5.86			0.42		1.44		57.0		69.1
60102		6.63			0.44		1.68		56.1		90.4
60103		7.76			0.66		1.89		74.0		110.7
60104		6.76			0.52		1.76		71.1		99.1
60105		7.06			0.50		1.65		75.5		86.3
60106			7.45		0.49		1.72		64.1		100.8
60107			7.50		0.57		1.85		73.7		113.8
60108			6.14		0.43		1.62		62.2		95.5
60109			7.69		0.60		1.65		77.3		94.9
60110			6.97		0.57		1.76		66.1		74.4

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Appendix 15 - 6 Organ Weight      CB      0.5 mg/kg      Female

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys		Adrenals		Ovaries	
	g	Day 29	g	Day 29	mg	Day 29	mg	Day 29	g	Day 29	g	Day 29	g	Day 29	g	Day 29	mg	Day 29	mg	Day 29
60201	196		1.85		21.0		456		0.73		5.77		0.43		1.47		56.4		82.4	
60202	247		1.83		20.3		518		0.92		7.76		0.52		1.97		77.6		111.4	
60203	213		1.73		17.7		579		0.83		6.39		0.55		1.72		75.2		80.2	
60204	233		1.89		16.5		428		0.89		6.84		0.53		1.54		73.5		93.9	
60205	192		1.88		19.0		551		0.69		5.45		0.42		1.52		53.1		74.9	

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Appendix 15 - 7 Organ Weight

C B I

5 mg/kg

Female

Animal Number	Final Body Weight		Brain	Thyroids	Thymus	Heart	Liver	Spleen	Kidneys	Adrenals	Ovaries
	g	Day 29	g	mg	mg	g	Day 29	g	Day 29	mg	mg
60301	218		1.80	18.4	516	0.89	6.93	0.46	1.64	70.4	77.9
60302	206		1.80	17.4	477	0.85	6.75	0.46	1.79	57.9	93.4
60303	228		1.88	16.2	659	0.99	7.31	0.49	1.81	70.3	102.8
60304	198		1.84	25.0	485	0.76	6.68	0.46	1.35	57.7	76.0
60305	230		1.82	22.6	399	0.94	8.07	0.66	1.84	71.9	126.9

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Appendix 15 - 8 Organ Weight      **C B I**      50 mg/kg      Female

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart	
	g Day 29	g Day 43	g Day 29	g Day 43	mg Day 29	mg Day 43	mg Day 29	mg Day 43	g Day 29	g Day 43
60401	206		1.80		21.0		429		0.74	
60402	212		1.89		19.9		410		0.83	
60403	204		1.92		16.9		663		0.88	
60404	228		1.95		29.7		635		0.90	
60405	213		2.01		20.7		732		0.88	
60406		246		1.86		27.8		618		0.94
60407		246		1.86		26.2		605		1.08
60408		205		1.92		18.1		391		0.86
60409		214		1.83		17.3		422		0.85
60410		247		2.04		22.2		601		0.98
Liver		Spleen		Kidneys		Adrenals		Ovaries		
Animal Number	g Day 29	g Day 43	g Day 29	g Day 43	g Day 29	g Day 43	mg Day 29	mg Day 43	mg Day 29	mg Day 43
60401	11.20		0.37		1.81		49.4		86.4	
60402	13.09		0.52		1.65		69.0		89.5	
60403	11.92		0.60		1.79		67.0		98.1	
60404	13.68		0.56		1.98		66.8		90.2	
60405	12.39		0.60		1.90		59.4		102.6	
60406		11.31		0.46		1.86		80.8		107.6
60407		9.90		0.61		1.84		65.5		83.2
60408		9.38		0.37		1.57		66.9		82.9
60409		9.93		0.43		1.75		64.6		87.5
60410		11.22		0.45		1.87		65.8		104.5

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Appendix 16 - 1 Relative Organ Weight      C B I      0 mg/kg      Male

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart				
	g	Day 29	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	%	Day 29	Day 43
20101	310		0.62			4.5			167.4		0.37		
20102	278		0.72			9.4			138.1		0.38		
20103	351		0.56			8.0			139.0		0.36		
20104	332		0.65			6.7			224.1		0.39		
20105	332		0.64			6.9			150.9		0.37		
20106		415		0.51			7.7			122.4		0.35	
20107		403		0.51			7.4			159.1		0.31	
20108		364		0.55			9.3			177.5		0.42	
20109		388		0.55			8.2			117.8		0.43	
20110		410		0.53			6.9			131.7		0.36	
Liver			Spleen		Kidneys		Adrenals		Testes				
Animal Number	%	Day 29	%	Day 29	Day 43	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	%	Day 29	Day 43
20101	2.94		0.25			0.80			20.3		1.08		
20102	2.79		0.19			0.87			15.2		1.15		
20103	2.81		0.18			0.77			18.5		0.89		
20104	3.03		0.22			0.86			19.3		0.98		
20105	3.04		0.21			0.79			14.9		0.96		
20106		2.75		0.17			0.77			16.4		0.90	
20107		2.76		0.15			0.78			15.6		0.85	
20108		2.84		0.18			0.71			16.4		0.81	
20109		2.82		0.26			0.80			13.0		0.89	
20110		2.71		0.18			0.85			11.8		0.90	

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Appendix 16 - 1 Relative Organ Weight

[ C B ] 0 mg/kg

Male

Epididymides

Animal Number	%	
	Day 29	Day 43
20101	0.25	
20102	0.26	
20103	0.24	
20104	0.24	
20105	0.24	
20106		0.30
20107		0.26
20108		0.23
20109		0.27
20110		0.30

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Appendix 16 - 2 Relative Organ Weight

C B I

0.5 mg/kg

Male

Animal Number	Final Body Weight		Brain	Thyroids	Thymus	Heart	Liver	Spleen	Kidneys	Adrenals	Testes	Epididymides
	g	%	x10 <sup>-3</sup> %	x10 <sup>-3</sup> %	%	%	%	%	x10 <sup>-3</sup> %	%	%	%
	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29
20201	347	0.56	6.7	220.2	0.33	4.69	0.20	0.89	17.3	0.89	0.21	
20202	296	0.65	6.6	189.5	0.35	5.11	0.18	0.81	17.9	1.10	0.25	
20203	360	0.57	7.1	143.1	0.34	5.02	0.24	0.84	14.2	0.87	0.21	
20204	294	0.67	8.6	186.4	0.34	5.80	0.23	0.79	16.9	1.10	0.28	
20205	336	0.60	4.7	159.2	0.33	5.07	0.21	0.79	16.6	0.95	0.22	

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Appendix 16 - 3 Relative Organ Weight      C B      5 mg/kg      Male

Animal Number	Final Body Weight g	Brain		Thyroids		Thymus		Heart		Liver		Spleen		Kidneys		Adrenals		Testes		Epididymides	
		Day 29	%	Day 29	x10 <sup>-3</sup> %	Day 29	x10 <sup>-3</sup> %	Day 29	%	Day 29	%	Day 29	%	Day 29	x10 <sup>-3</sup> %	Day 29	%	Day 29	%	Day 29	%
20301	320	0.60	9.4	212.2	0.40	7.65	0.28	0.95	16.4	1.04	0.23										
20302	307	0.67	7.4	145.9	0.40	7.58	0.20	0.94	14.8	1.18	0.24										
20303	283	0.67	10.0	179.9	0.39	8.35	0.24	0.82	16.8	1.11	0.27										
20304	320	0.61	8.4	157.8	0.38	7.74	0.26	0.95	16.6	1.04	0.23										
20305	372	0.53	7.7	153.8	0.35	7.74	0.24	0.87	14.1	0.86	0.19										

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Appendix 16 - 4 Relative Organ Weight

G-B 50 mg/kg

Male

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart	
	g	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43
20401	231			0.84		9.7		141.1		0.36
20402	269			0.74		9.3		148.0		0.41
20403	243			0.80		15.0		216.0		0.37
20404	246			0.74		9.8		132.9		0.37
20405	301			0.61		8.5		166.8		0.39
20406		349			0.58		7.1		149.3	0.40
20407		401			0.57		7.9		126.7	0.37
20408		361			0.54		8.3		193.4	0.36
20409		338			0.54		10.0		182.0	0.38
20410		376			0.52		6.6		114.4	0.37
Liver			Spleen		Kidneys		Adrenals		Testes	
Animal Number	%	%	Day 29	Day 43	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43
20401	8.25			0.19		1.03		19.1		1.45
20402	8.62			0.19		0.96		17.0		1.28
20403	8.85			0.19		0.82		18.6		1.28
20404	8.66			0.17		0.93		21.6		1.28
20405	8.35			0.22		0.85		15.5		0.98
20406		6.05			0.23		0.81		16.9	1.09
20407		4.61			0.22		0.76		17.3	0.91
20408		5.34			0.23		0.83		17.4	1.21
20409		4.70			0.20		0.75		19.3	0.98
20410		5.13			0.20		0.74		16.4	0.91

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Appendix 16 - 4 Relative Organ Weight

CB 50 mg/kg Male

Epididymides

Animal Number	% Day 29	% Day 43
20401	0.35	
20402	0.28	
20403	0.27	
20404	0.27	
20405	0.24	
20406		0.32
20407		0.30
20408		0.27
20409		0.30
20410		0.26

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Appendix 16 - 5 Relative Organ Weight

C B I

0 mg/kg

Female

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart		
	g	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43	
60101	192			1.01		10.0		325.5		0.41	
60102	213			0.89		8.5		249.8		0.42	
60103	238			0.76		8.9		222.7		0.41	
60104	218			0.89		7.4		256.9		0.41	
60105	221			0.84		7.8		188.2		0.37	
60106		265			0.71		7.1		198.5	0.35	
60107		247			0.78		9.0		123.5	0.40	
60108		219			0.87		11.4		205.9	0.46	
60109		250			0.76		9.4		263.2	0.39	
60110		231			0.86		7.4		236.4	0.45	
Liver			Spleen		Kidneys		Adrenals		Ovaries		
Animal Number	%	%	Day 29	Day 43	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	x10 <sup>-3</sup> %	Day 43
60101	3.05			0.22		0.75		29.7		36.0	
60102	3.11			0.21		0.79		26.3		42.4	
60103	3.26			0.28		0.79		31.1		46.5	
60104	3.10			0.24		0.81		32.6		45.5	
60105	3.19			0.23		0.75		34.2		39.0	
60106		2.81			0.18		0.65		24.2		38.0
60107		3.04			0.23		0.75		29.8		46.1
60108		2.80			0.20		0.74		28.4		43.6
60109		3.08			0.24		0.66		30.9		38.0
60110		3.02			0.25		0.76		28.6		32.2

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Appendix 16 - 6 Relative Organ Weight

CB

0.5 mg/kg

Female

Animal Number	Final Body Weight g	Brain %		Thyroids $\times 10^{-3}\%$		Thymus $\times 10^{-3}\%$		Heart %		Liver %		Spleen %		Kidneys %		Adrenals $\times 10^{-3}\%$		Ovaries $\times 10^{-3}\%$	
		Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	Day 29	
60201	196	0.94		10.7		232.7		0.37		2.94		0.22		0.75		28.8		42.0	
60202	247	0.74		8.2		209.7		0.37		3.14		0.21		0.80		31.4		45.1	
60203	213	0.81		8.3		271.8		0.39		3.00		0.26		0.81		35.3		37.7	
60204	233	0.81		7.1		183.7		0.38		2.94		0.23		0.66		31.5		40.3	
60205	192	0.98		9.9		287.0		0.36		2.84		0.22		0.79		27.7		39.0	

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Appendix 16 - 7 Relative Organ Weight

C B I

5 mg/kg

Female

Animal Number	Final Body Weight		Brain	Thyroids	Thymus	Heart	Liver	Spleen	Kidneys	Adrenals	Ovaries
	g	%	x10 <sup>-3</sup> % Day 29	x10 <sup>-3</sup> % Day 29	x10 <sup>-3</sup> % Day 29	x10 <sup>-3</sup> % Day 29	x10 <sup>-3</sup> % Day 29				
60301	218	0.83	8.4	236.7	0.41	3.18	0.21	0.75	32.3	32.3	35.7
60302	206	0.87	8.4	231.6	0.41	3.28	0.22	0.87	28.1	28.1	45.3
60303	228	0.82	7.1	289.0	0.43	3.21	0.21	0.79	30.8	30.8	45.1
60304	198	0.93	12.6	244.9	0.38	3.37	0.23	0.68	29.1	29.1	38.4
60305	230	0.79	9.8	173.5	0.41	3.51	0.29	0.80	31.3	31.3	55.2

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Appendix 16 - 8 Relative Organ Weight

C B I

50 mg/kg

Female

Animal Number	Final Body Weight		Brain		Thyroids		Thymus		Heart	
	g	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43
60401	206			0.87		10.2		208.3		0.36
60402	212			0.89		9.4		193.4		0.39
60403	204			0.94		8.3		325.0		0.43
60404	228			0.86		13.0		278.5		0.39
60405	213			0.94		9.7		343.7		0.41
60406			246		0.76		11.3		251.2	
60407			246		0.76		10.7		245.9	
60408			205		0.94		8.8		190.7	
60409			214		0.86		8.1		197.2	
60410			247		0.83		9.0		243.3	
Liver			Spleen		Kidneys		Adrenals		Ovaries	
Animal Number	%	%	Day 29	Day 43	%	Day 29	Day 43	x10 <sup>-3</sup> %	Day 29	Day 43
	5.44				0.18			24.0		
60401	5.44				0.18			24.0		41.9
60402	6.17				0.25			32.5		42.2
60403	5.84				0.29			32.8		48.1
60404	6.00				0.25			29.3		39.6
60405	5.82				0.28			27.9		48.2
60406			4.60		0.19		0.76		32.8	
60407			4.02		0.25		0.75		26.6	
60408			4.58		0.18		0.77		32.6	
60409			4.64		0.20		0.82		30.2	
60410			4.54		0.18		0.76		26.6	

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Appendix 17 - 1 Pathological Findings      C B I      0 mg/kg      Male

Animal No.	Necropsy Findings	Histological Findings
20101 SS (5W)	Finding absent	Lung (and bronchus) Mineralization, arterial wall, focal(1) Liver Cell infiltration, lymphocyte, focal(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Kidney, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Thyroid, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball
20102 SS (5W)	Finding absent	Heart Cell infiltration, lymphocyte, focal(1) Liver Cell infiltration, lymphocyte, focal(1) Kidney Basophilic tubule, proximal tubular epithelium, Bilateral(1) Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice

1 , Minimal

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Appendix 17 - 1 Pathological Findings

C B I

0 mg/kg

Male

Animal No.		Necropsy Findings	Histological Findings
20103	SS (5W)	Finding absent	<p>Stomach Erosion, glandular stomach, focal(1)</p> <p>Kidney Basophilic tubule, proximal tubular epithelium, Bilateral(1)</p> <p>Thyroid Ectopic thymic tissue, Unilateral(1)</p> <p>Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Liver, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball</p>
20104	SS (5W)	Finding absent	<p>Kidney Basophilic tubule, proximal tubular epithelium, Unilateral(1)</p> <p>Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Liver, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Thyroid, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball</p>

SS , Scheduled sacrifice

1 , Minimal

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Appendix 17 - 1 Pathological Findings			C B I	0 mg/kg	Male
Animal No.		Necropsy Findings	Histological Findings		
20105	SS (5W)	Finding absent	Kidney Basophilic tubule, proximal tubular epithelium, Unilateral(1) Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Liver, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball		
20106	SS (7W)	Finding absent	Liver Cell infiltration, lymphocyte, focal(1) Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Adrenal		
20107	SS (7W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal		
20108	SS (7W)	Finding absent	Liver Cell infiltration, lymphocyte, focal(1) Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Adrenal		

SS , Scheduled sacrifice

1 , Minimal

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Appendix 17 - 1 Pathological Findings

CBI 0 mg/kg

Male

Animal No.		Necropsy Findings	Histological Findings
20109	SS (7W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal
20110	SS (7W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal

SS , Scheduled sacrifice

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Appendix 17 - 2 Pathological Findings			C B I	0.5 mg/kg	Male
Animal No.	Necropsy Findings		Histological Findings		
20201	SS (5W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Finding absent : Adrenal		
20202	SS (5W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Thyroid		
20203	SS (5W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Thyroid		
20204	SS (5W)	Liver Brownish change(+) Enlargement(+) Kidney Dilatation, pelvis, Unilateral(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Kidney Dilatation, pelvis, Unilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Thyroid		
20205	SS (5W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Finding absent : Thyroid, Adrenal		

SS , Scheduled sacrifice  
+ , Present; 1 , Minimal

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Appendix 17 - 3 Pathological Findings			C B I	5 mg/kg	Male
Animal No.		Necropsy Findings	Histological Findings		
20301	SS (5W)	Liver Enlargement(+)	Liver Extramедullary hematopoiesis, erythrocytic(1) Hypertrophy, hepatocyte, centrilobular(1)		
			Thyroid Hypertrophy, follicular cell, Bilateral(1)		
			Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilatral(1)		
20302	SS (5W)	Liver Brownish change(+) Enlargement(+) Whitish patch, a few(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1)		
			Thyroid Ultimobranchial remnant, Bilateral(1)		
			Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)		
20303	SS (5W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1)		
			Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)		
			Finding absent : Thyroid		
20304	SS (5W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1)		
			Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Unilateral(1)		
			Finding absent : Thyroid		

SS , Scheduled sacrifice  
+ , Present; 1 , Minimal

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Study No. B081041

Appendix 17 - 3 Pathological Findings

C B I 5 mg/kg Male

Animal No.	Necropsy Findings	Histological Findings
20305 SS (5W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Ultimobranchial remnant, Unilateral(1) Finding absent : Adrenal

SS , Scheduled sacrifice  
+ , Present; 1 , Minimal

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Study No. B081041

Appendix 17 - 4 Pathological Findings      C B I      50 mg/kg      Male

Animal No.	Necropsy Findings	Histological Findings
20401 SS (5W)	Liver Brownish change(+) Enlargement(+)	Liver Cell infiltration, lymphocyte, focal(1) Hyper trophy, hepatocyte, centrilobular(2) Thyroid Hyper trophy, follicular cell, Bilateral(1) Adrenal Hyper trophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Kidney, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Parathyroid, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice

+ , Present; 1 , Minimal; 2 , Mild

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Study No. B081041

Appendix 17 - 4 Pathological Findings      [CB] 50 mg/kg      Male

Animal No.	Necropsy Findings	Histological Findings
20402 SS (5W)	Liver Brownish change(+) Enlargement(+) Whitish patch, a few(+)	Heart Cell infiltration, lymphocyte, focal(1) Liver Brown pigment deposition, macrophage, focal(1) Granuloma(2) Hypertrophy, hepatocyte, centrilobular(2) Necrosis, hepatocyte, focal(1) Kidney Cell infiltration, lymphocyte, interstitium, Unilateral(1) Thyroid Ultimobranchial remnant, Unilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Parathyroid, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice

+ , Present; 1 , Minimal; 2 , Mild

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Study No. B081041

Appendix 17 - 4 Pathological Findings      C B I      50 mg/kg      Male

Animal No.	Necropsy Findings	Histological Findings
20403 SS (SW)	Liver Brownish change(+) Enlargement(+) Whitish patch, many(+)	Liver Brown pigment deposition, macrophage, focal(1) Hypertrophy, hepatocyte, centrilobular(2) Necrosis, hepatocyte, focal(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Kidney, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Thyroid, Parathyroid, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice

+ , Present; 1 , Minimal; 2 , Mild

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Study No. B081041

Appendix 17 - 4 Pathological Findings

C B I

50 mg/kg

Male

Animal No.	Necropsy Findings	Histological Findings
20404 SS (5W)	Liver Brownish change(+) Enlargement(+) Whitish patch, many(+)	Lung (and bronchus) Accumulation, foam cell, focal(1) Liver Brown pigment deposition, macrophage, focal(1) Hypertrophy, hepatocyte, centrilobular(2) Necrosis, hepatocyte, focal(1) Kidney Basophilic tubule, proximal tubular epithelium, Unilateral(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Ultimobranchial remnant, Unilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Parathyroid, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice

+ , Present; 1 , Minimal; 2 , Mild

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Study No. B081041

Appendix 17 - 4 Pathological Findings      C B I      50 mg/kg      Male

Animal No.		Necropsy Findings	Histological Findings
20405	SS (5W)	Liver Brownish change(+) Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(2) Necrosis, hepatocyte, focal(1) Kidney Basophilic tubule, proximal tubular epithelium, Bilateral(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Testis, Epididymis, Prostate, Pituitary, Parathyroid, Brain, Spinal cord, Sciatic nerve, Eyeball
20406	SS (7W)	Liver Enlargement(+) Whitish patch, many(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1) Proliferation, bile duct, focal(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Thyroid

SS , Scheduled sacrifice

+ , Present; 1 , Minimal; 2 , Mild

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Study No. B081041

Appendix 17 - 4 Pathological Findings      CB      50 mg/kg      Male

Animal No.		Necropsy Findings	Histological Findings
20407	SS (7W)	Liver Enlargement(+) Whitish patch, one(+)	Liver Brown pigment deposition, macrophage, focal(1) Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1) Proliferation, bile duct, focal(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)
20408	SS (7W)	Liver Enlargement(+) Testis Asymmetry(+) Thyroid Nodule, one, Unilateral(+)	Liver Brown pigment deposition, macrophage, focal(1) Extramedullary hematopoiesis, erythrocytic(1) Hypertrophy, hepatocyte, centrilobular(1) Proliferation, bile duct, focal(1) Testis Dilatation, seminiferous tubule, diffuse, Unilateral(1) Thyroid Ectopic thymic tissue, Unilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)
20409	SS (7W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Adrenal <u>Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)</u>

SS , Scheduled sacrifice  
+ , Present; 1 , Minimal

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Study No. B081041

Appendix 17 - 4 Pathological Findings

C.B.I.

50 mg/kg

Male

Animal No.	Necropsy Findings		Histological Findings
20410	SS (7W)	Liver Enlargement(+)	Liver Brown pigment deposition, macrophage, focal(1) Hypertrophy, hepatocyte, centrilobular(1) Proliferation, bile duct, focal(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Ultimobranchial remnant, Unilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)

SS , Scheduled sacrifice

+ , Present; l , Minimal

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Study No. B081041

Appendix 17 - 5 Pathological Findings      [ C B I ]      0 mg/kg      Female

Animal No.	Necropsy Findings	Histological Findings
60101 SS (5W)	Finding absent	Thyroid Ultimobranchial remnant, Bilateral(1) Eyeball Dysplasia, retina, focal(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Liver, Kidney, Urinary bladder, Ovary, Uterus, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve
60102 SS (5W)	Finding absent	Heart Cell infiltration, lymphocyte, focal(1) Kidney Basophilic tubule, proximal tubular epithelium, Bilateral(1) Dilatation, distal tubule, Bilateral(1) Finding absent : Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Liver, Urinary bladder, Ovary, Uterus, Pituitary, Thyroid, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice  
1 , Minimal

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Study No. B081041

Appendix 17 - 5 Pathological Findings			C B I	0 mg/kg	Female
Animal No.	Necropsy Findings		Histological Findings		
60103	SS (5W)	Finding absent	Kidney Basophilic tubule, proximal tubular epithelium, Unilateral(1) Thyroid Ultimobranchial remnant, Bilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Liver, Urinary bladder, Ovary, Uterus, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball		
60104	SS (5W)	Finding absent	Large intestine, colon Cell infiltration, lymphocyte, focal(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, rectum, Liver, Kidney, Urinary bladder, Ovary, Uterus, Pituitary, Thyroid, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball		

SS , Scheduled sacrifice  
1 , Minimal

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Study No. B081041

Appendix 17 - 5 Pathological Findings

CB

0 mg/kg

Female

Animal No.	Necropsy Findings	Histological Findings
60105 SS (5W)	Finding absent	Liver Cell infiltration, lymphocyte, focal(1) Kidney Basophilic tubule, proximal tubular epithelium, Bilateral(1) Adrenal Necrosis, cortical cell, focal, Bilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Ovary, Uterus, Pituitary, Thyroid, Parathyroid, Brain, Spinal cord, Sciatic nerve, Eyeball
60106 SS (7W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal
60107 SS (7W)	Finding absent	Thyroid Ultimobranchial remnant, Bilateral(1) Finding absent : Liver, Adrenal
60108 SS (7W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal
60109 SS (7W)	Finding absent	Thyroid Ultimobranchial remnant, Bilateral(1) Finding absent : Liver, Adrenal

SS , Scheduled sacrifice

1 , Minimal

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Study No. B081041

Appendix 17 - 5 Pathological Findings      [CB] 0 mg/kg      Female

Animal No.	Necropsy Findings	Histological Findings
60110 SS (7W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal

SS , Scheduled sacrifice

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Study No. B081041

Appendix 17 - 6 Pathological Findings      C B I      0.5 mg/kg      Female

Animal No.		Necropsy Findings	Histological Findings
60201	SS (5W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal
60202	SS (5W)	Finding absent	Thyroid Ultimobranchial remnant, Bilateral(1) Finding absent : Liver, Adrenal
60203	SS (5W)	Finding absent	Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Liver, Adrenal
60204	SS (5W)	Finding absent	Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Liver, Adrenal
60205	SS (5W)	Finding absent	Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Liver, Adrenal

SS , Scheduled sacrifice

1 , Minimal

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Study No. B081041

Appendix 17 - 7 Pathological Findings

C B I

5 mg/kg

Female

Animal No.		Necropsy Findings	Histological Findings
60301	SS (5W)	Finding absent	Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Liver, Adrenal
60302	SS (5W)	Finding absent	Liver Cell infiltration, lymphocyte, focal(1) Finding absent : Thyroid, Adrenal
60303	SS (5W)	Finding absent	Finding absent : Liver, Thyroid, Adrenal
60304	SS (5W)	Finding absent	Liver Cell infiltration, lymphocyte, focal(1) Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Adrenal
60305	SS (5W)	Finding absent	Liver Cell infiltration, lymphocyte, focal(1) Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Adrenal

SS , Scheduled sacrifice  
1 , Minimal

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Study No. B081041

Appendix 17 - 8 Pathological Findings

C B I 50 mg/kg

Female

Animal No.	Necropsy Findings	Histological Findings
60401 SS (5W)	Liver Brownish change(+) Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1) Kidney Basophilic tubule, proximal tubular epithelium, Unilateral(1) Thyroid Ultimobranchcal remnant, Unilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Ovary, Uterus, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice  
+, Present; 1 , Minimal

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Study No. B081041

Appendix 17 - 8 Pathological Findings      [ C B ]      50 mg/kg      Female

Animal No.		Necropsy Findings	Histological Findings
60402	SS (5W)	Liver Brownish change(+) Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Kidney Fibrosis, focal, Unilateral(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Ultimobranchial remnant, Unilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Ovary, Uterus, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice  
+ , Present; 1 , Minimal

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Study No. B081041

Appendix 17 - 8 Pathological Findings      C B I      50 mg/kg      Female

Animal No.	Necropsy Findings	Histological Findings
60403 SS (5W)	Liver Brownish change(+) Enlargement(+)  Thyroid Defect, Unilateral(+) Enlargement, Unilateral(+)	Stomach Cell infiltration, eosinophil, submucosa, focal(1) Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1) Thyroid Hypertrophy, follicular cell, Unilateral(1) Ultimobranchial remnant, Unilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Kidney, Urinary bladder, Ovary, Uterus, Pituitary, Parathyroid, Adrenal, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice  
+ , Present; 1 , Minimal

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Study No. B081041

Appendix 17 - 8 Pathological Findings      C B I      50 mg/kg      Female

Animal No.		Necropsy Findings	Histological Findings
60404	SS (5W)	Liver Brownish change(+) Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Kidney Basophilic tubule, proximal tubular epithelium, Bilateral(1) Thyroid Ultimobranchial remnant, Bilateral(1) Adrenal Accessory adrenocortical tissue, Unilateral(1) Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Ovary, Uterus, Pituitary, Parathyroid, Brain, Spinal cord, Sciatic nerve, Eyeball

SS , Scheduled sacrifice  
+ , Present; I , Minimal

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Study No. B081041

Appendix 17 - 8 Pathological Findings			C B I	50 mg/kg	Female
Animal No.	Necropsy Findings		Histological Findings		
60405 SS (5W)	Liver	Brownish change(+) Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Necrosis, hepatocyte, focal(1)		
	Thyroid	Defect, Unilateral(+) Enlargement, Unilateral(+)	Kidney Basophilic tubule, proximal tubular epithelium, Bilateral(1) Thyroid Hypertrophy, follicular cell, Unilateral(1)		
			Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Eyeball Dysplasia, retina, focal(1)		
			Finding absent : Heart, Lymph node, mandibular, Lymph node, mesenteric, Thymus, Spleen, Bone marrow, femur, Trachea, Lung (and bronchus), Stomach, Small intestine, duodenum, Small intestine, jejunum, Small intestine, ileum, Large intestine, cecum, Large intestine, colon, Large intestine, rectum, Urinary bladder, Ovary, Uterus, Pituitary, Parathyroid, Brain, Spinal cord, Sciatic nerve		
60406 SS (7W)	Liver	Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Thyroid Hypertrophy, follicular cell, Bilateral(1) Ultimobranchial remnant, Unilateral(1)		
			Finding absent : Adrenal		

SS , Scheduled sacrifice  
+ , Present; 1 , Minimal

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Study No. B081041

Appendix 17 - 8 Pathological Findings			C B I	50 mg/kg	Female
Animal No.	Necropsy Findings		Histological Findings		
60407	SS (7W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Thyroid Ultimobranchial remnant, Unilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)		
60408	SS (7W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Thyroid Ultimobranchial remnant, Unilateral(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1)		
60409	SS (7W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Thyroid Ultimobranchial remnant, Unilateral(1) Finding absent : Adrenal		
60410	SS (7W)	Liver Enlargement(+)	Liver Hypertrophy, hepatocyte, centrilobular(1) Adrenal Hypertrophy, cortical cell, glomerular zone, diffuse, Bilateral(1) Finding absent : Thyroid		

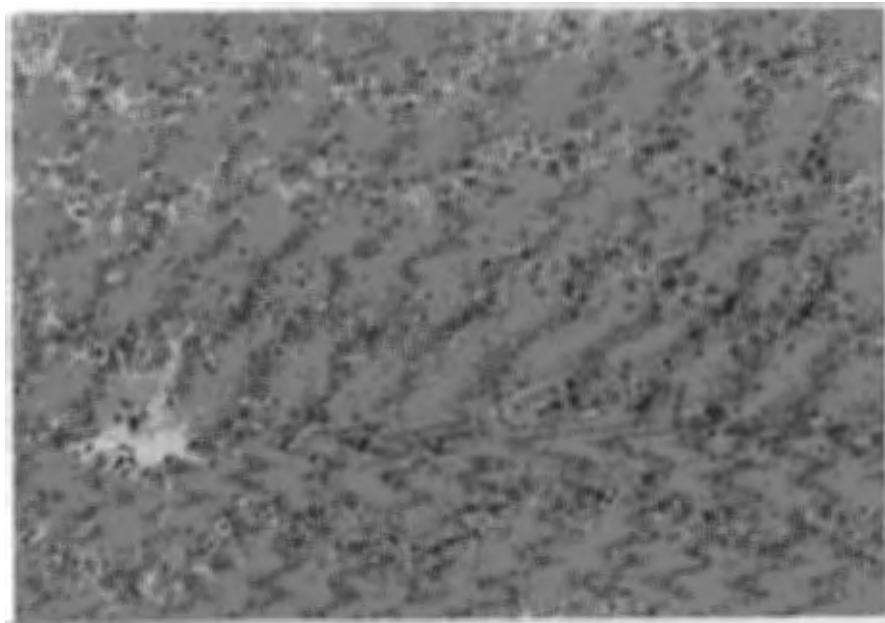
SS , Scheduled sacrifice  
+, Present; 1 , Minimal

**CONFIDENTIAL**

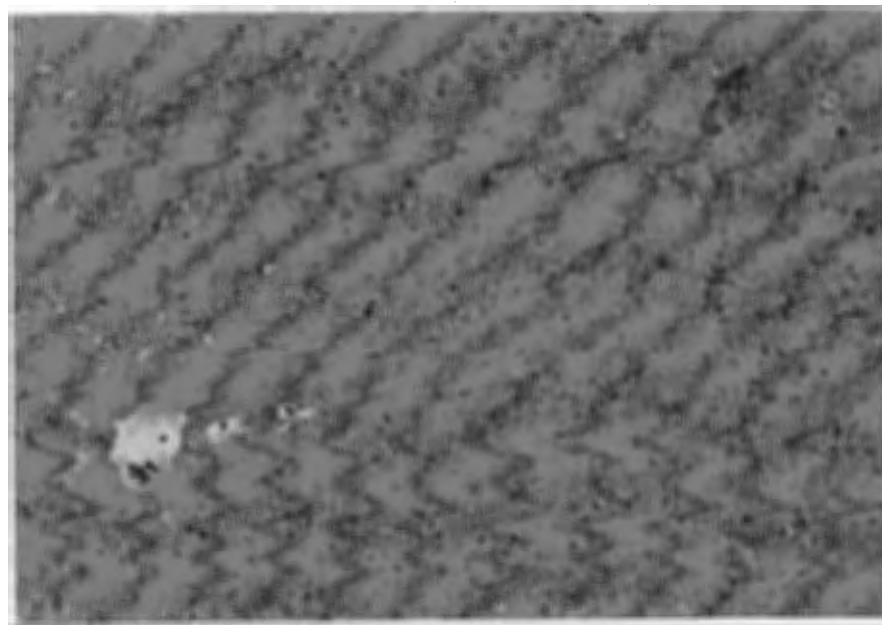
Photographs 1-14

(Study No. B081041)

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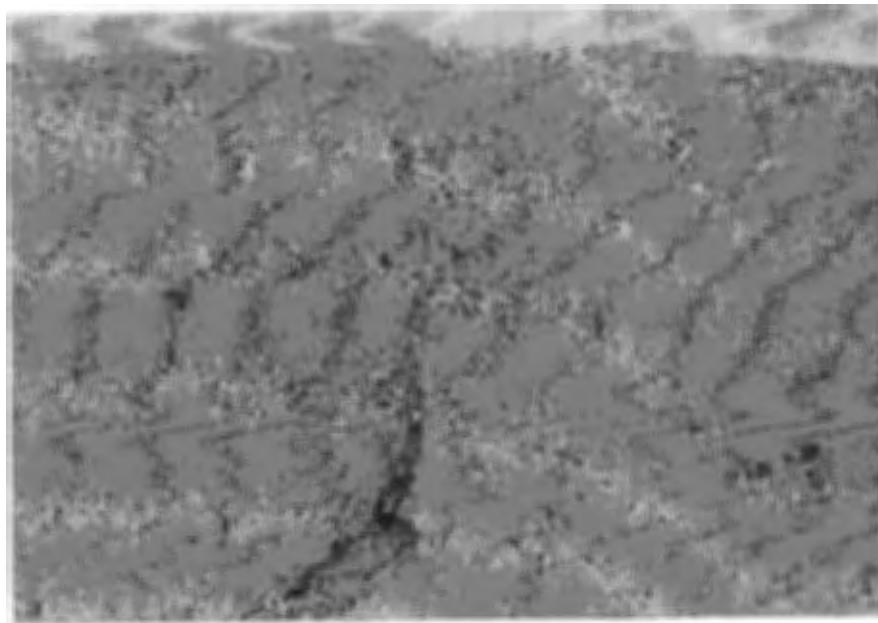


Photograph 1.  
Control group, Male, Animal No.20101 (Scheduled sacrifice)  
Liver: No remarkable change. (HE, x 200)



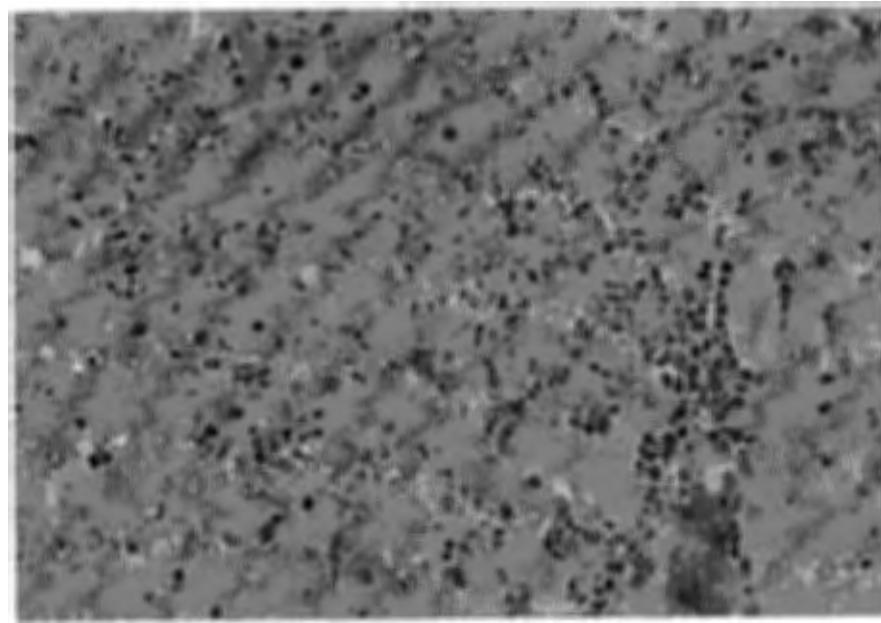
Photograph 2.  
[REDACTED] CBI 50 mg/kg group, Male, Animal No.20401 (Scheduled sacrifice)  
Liver: Hypertrophy of centrilobular hepatocyte, mild in grade. (HE, x 200)

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Photograph 3.

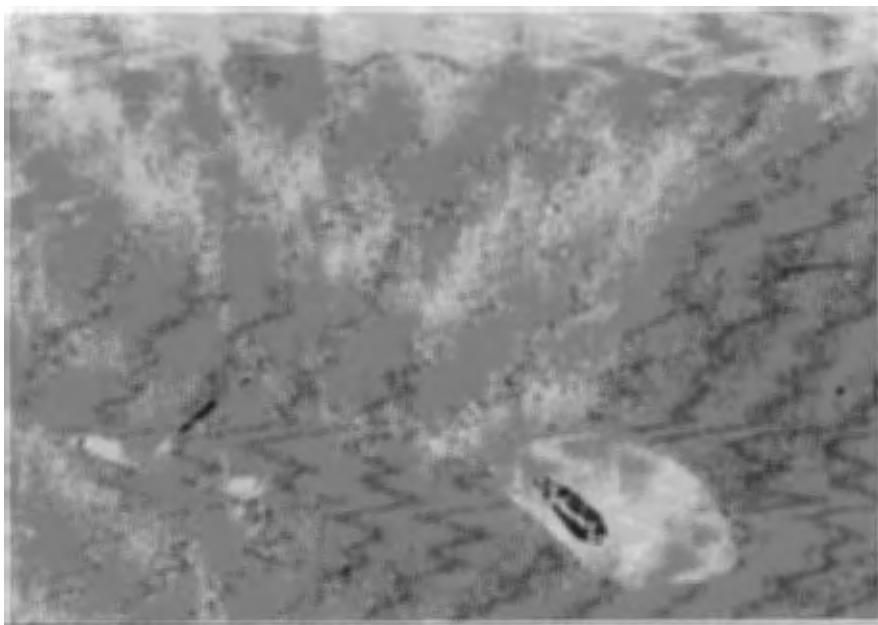
[CBI] 50 mg/kg group, Male, Animal No.20404 (Scheduled sacrifice)  
Liver: Focal necrosis, minimal in grade. (HE, x 100)



Photograph 4

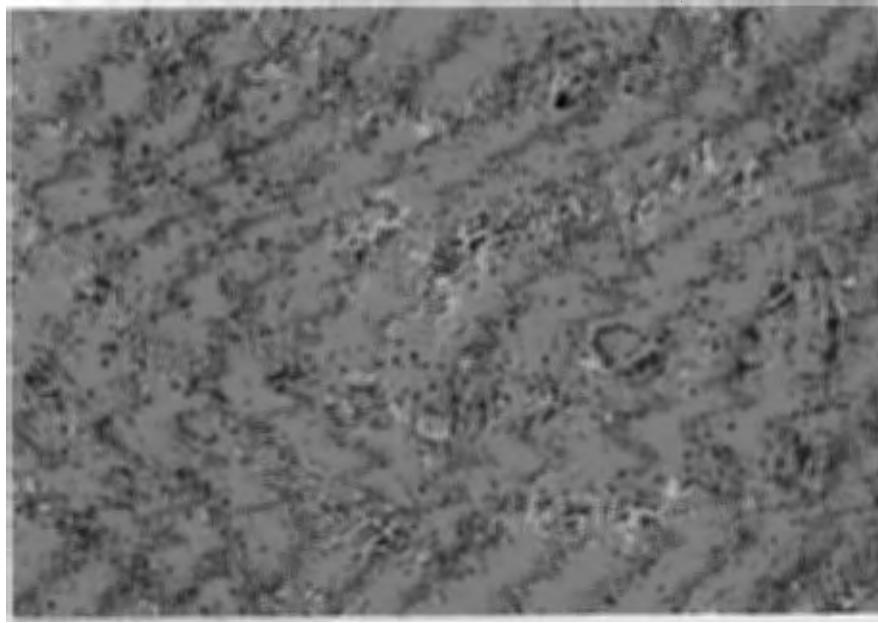
[CBI] 50 mg/kg group, Male, Animal No.20404 (Scheduled sacrifice)  
Liver: Focal necrosis, minimal in grade. Higher magnification photograph 3.  
(HE, x 400)

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Photograph 5.

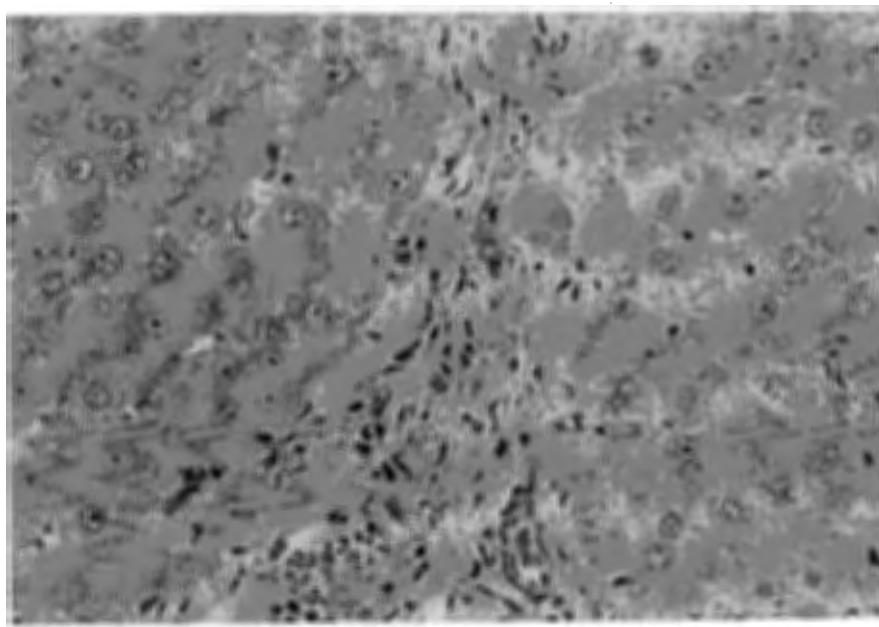
CBI 50 mg/kg group, Male, Animal No.20402 (Scheduled sacrifice)  
Liver: Granuloma, mild in grade. (HE, x 40)



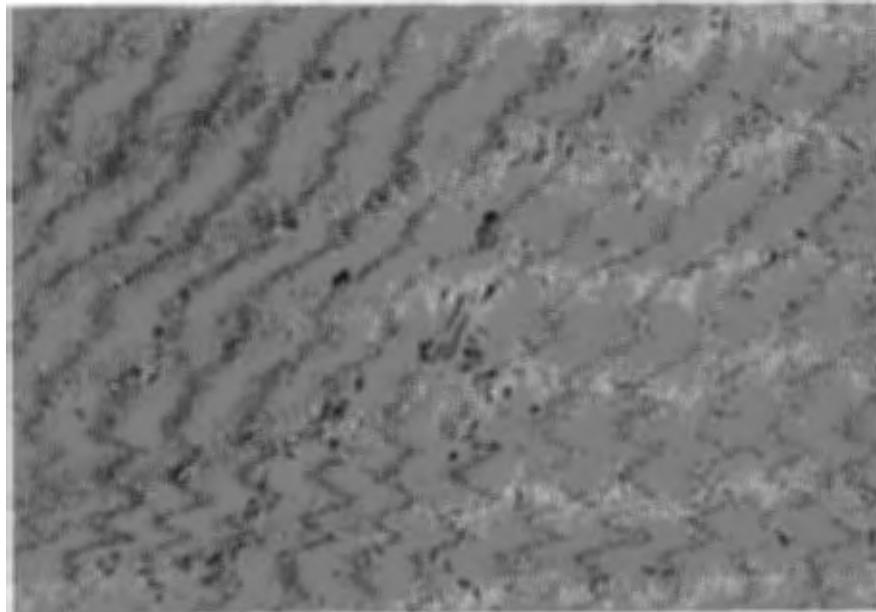
Photograph 6.

CBI 50 mg/kg group, Male, Animal No.20402 (Scheduled sacrifice)  
Liver: Granuloma, mild in grade. Higher magnification photograph 5. (HE, x 200)

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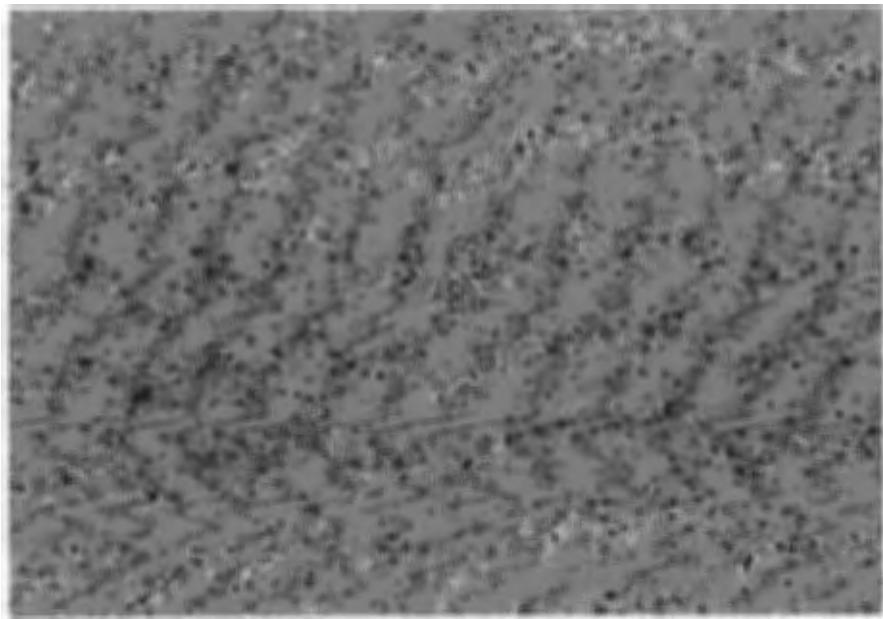


Photograph 7.  
CBI 50 mg/kg group, Male, Animal No.20402 (Scheduled sacrifice)  
Liver: Brown pigment deposition, macrophage, focal , minimal in grade. (HE, x 400)

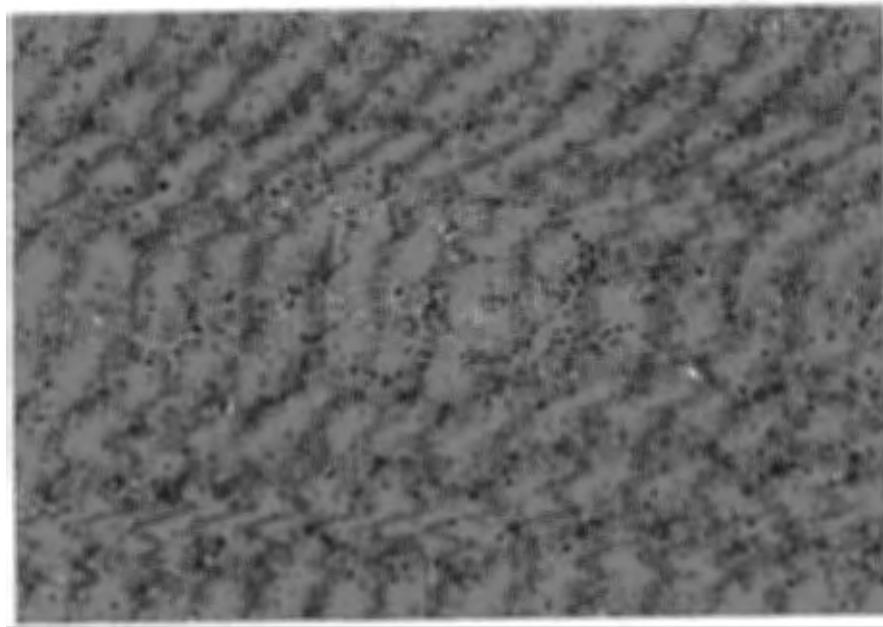


Photograph 8.  
CBI 50 mg/kg group, Male, Animal No.20402 (Scheduled sacrifice)  
Liver: Pigments react positively to Berlin blue. (Berlin blue, x 400)

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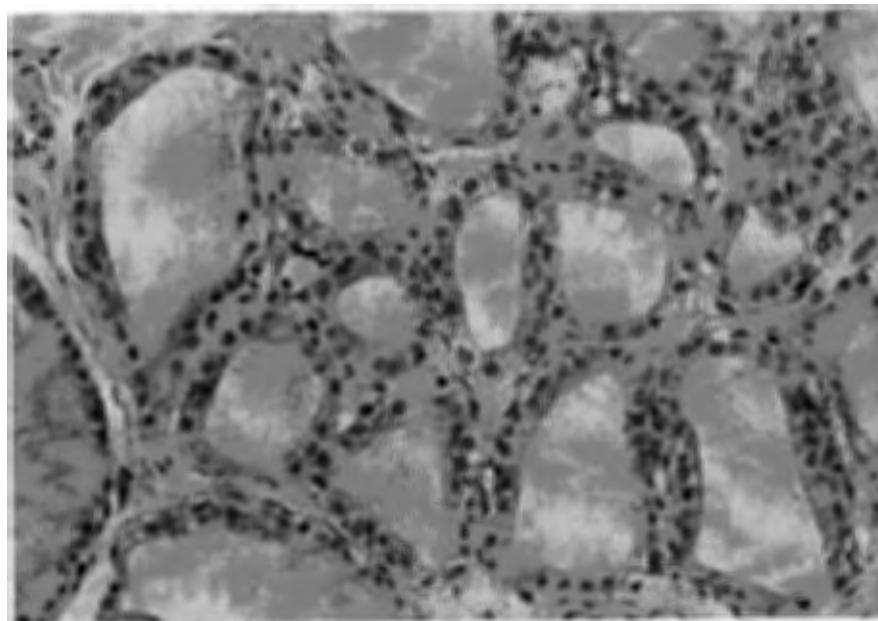


Photograph 9.  
Control group, male, Animal No.20107 (Scheduled sacrifice (Recovery))  
Liver: No remarkable change. (HE, x 200)

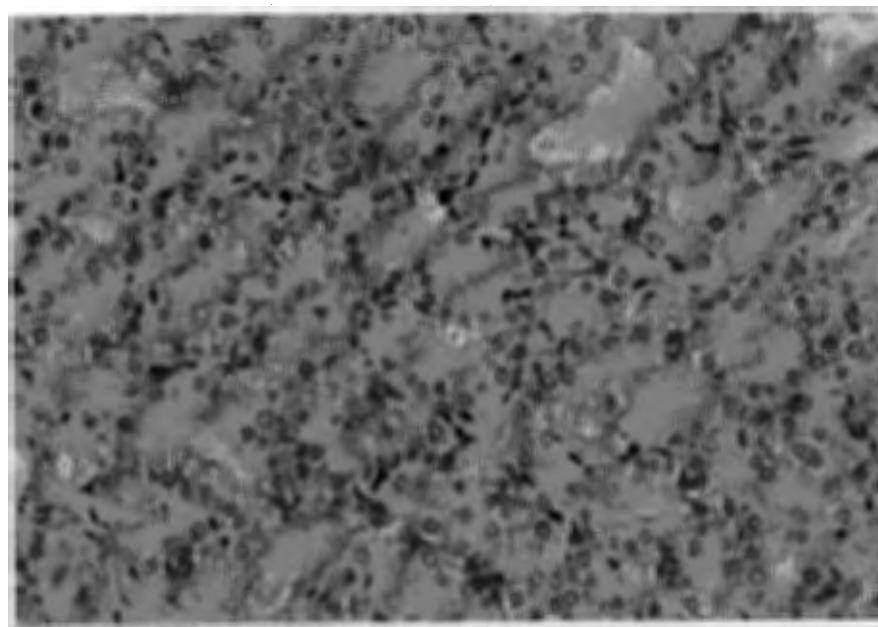


Photograph 10.  
[REDACTED] 50 mg/kg group, Male, Animal No.20408(Scheduled sacrifice(Recovery))  
Liver: Proliferation of bile duct, minimal in grade. (HE, x 200)

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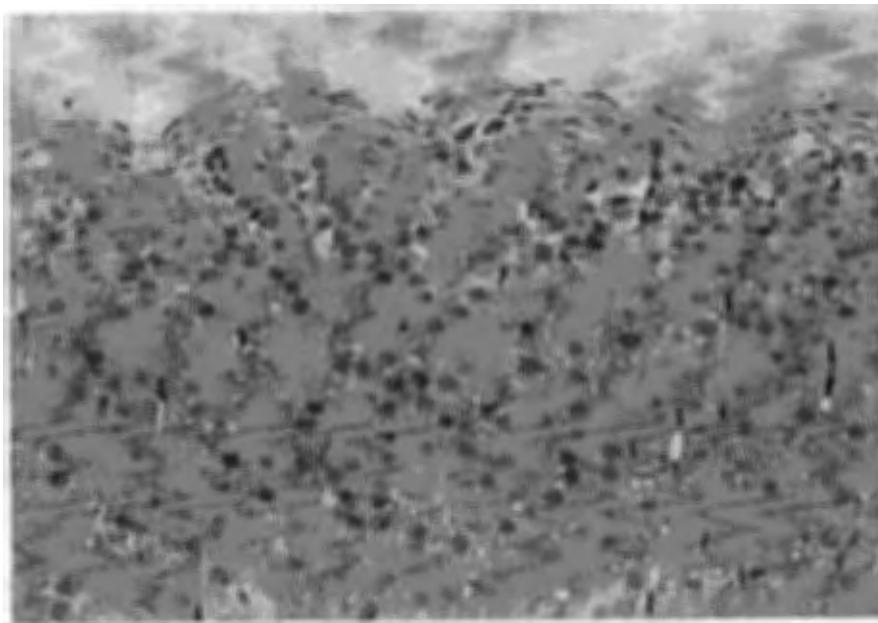


Photograph 11.  
Control group, male, Animal No.20105 (Scheduled sacrifice)  
Thyroid: No remarkable change. (HE, x 400)

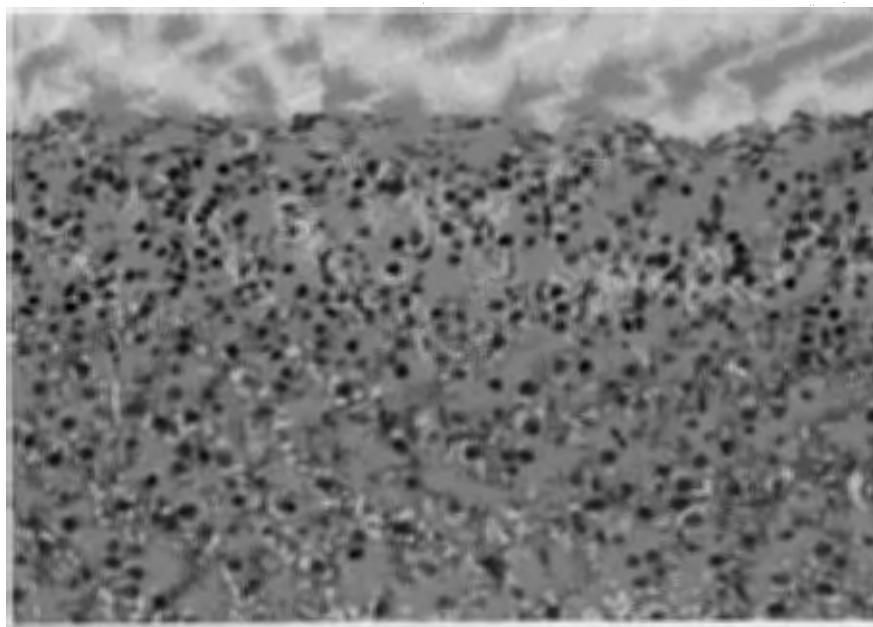


Photograph 12.  
[REDACTED] 50 mg/kg group, male, Animal No.20404 (Scheduled sacrifice)  
Thyroid: Hypertrophy of follicular cell, minimal in grade. (HE, x 400)

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Photograph 13.  
Control group, male, Animal No.20101 (Scheduled sacrifice)  
Adrenal: No remarkable change. (HE, x 400)



Photograph 14.  
[REDACTED] 50 mg/kg group, male, Animal No.20403 (Scheduled sacrifice)  
Adrenal: Diffuse hypertrophy of glomerulosa cell, minimal in grade. (HE, x 400)

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B081041

## Quality Assurance Statement

Sponsor: [REDACTED] (CBI)  
Title: A 28-Day Repeated Dose Oral Toxicity Study of [REDACTED] (CBI) in Rats  
Study No.: B081041

This study was carried out in accordance with the following standard. I hereby certify that this final report faithfully describes the methods and results in this study. The inspection and reporting are as follows.

Standards Concerning Testing Facilities Implementing Studies Related to New Chemical Substances

Inspection	Inspector	Inspection Date	Reporting Date to the Study Director	Reporting Date to the Management
<b>Study Protocol</b>				
Draft Study Protocol	[REDACTED]	Oct. 17, 2008	Oct. 17, 2008	Oct. 17, 2008
(Re-inspection)	[REDACTED]	Oct. 20, 2008	Oct. 20, 2008	Oct. 20, 2008
Study Protocol	[REDACTED]	Oct. 21, 2008	Oct. 21, 2008	Oct. 21, 2008
MiTOX protocol	[REDACTED]	Oct. 21, 2008	Oct. 21, 2008	Oct. 21, 2008
Draft Amendment No. 1	[REDACTED]	Oct. 27, 2008	Oct. 27, 2008	Oct. 27, 2008
Amendment No. 1	[REDACTED]	Oct. 28, 2008	Oct. 28, 2008	Oct. 28, 2008
Draft Amendment No. 2	[REDACTED]	Nov. 26, 2008	Nov. 26, 2008	Nov. 26, 2008
Amendment No. 2	[REDACTED]	Dec. 01, 2008	Dec. 01, 2008	Dec. 01, 2008
Draft Amendment No. 3	[REDACTED]	Dec. 17, 2008	Dec. 17, 2008	Dec. 17, 2008
Amendment No. 3	[REDACTED]	Dec. 17, 2008	Dec. 17, 2008	Dec. 17, 2008
Draft Amendment No. 4	[REDACTED]	Jan. 23, 2009	Jan. 23, 2009	Jan. 23, 2009
Amendment No. 4	[REDACTED]	Jan. 23, 2009	Jan. 23, 2009	Jan. 23, 2009
Draft Amendment No. 5	[REDACTED]	Feb. 09, 2009	Feb. 09, 2009	Feb. 09, 2009
(Re-inspection)	[REDACTED]	Mar. 25, 2009	Mar. 25, 2009	Mar. 25, 2009
Amendment No. 5	[REDACTED]	Mar. 31, 2009	Mar. 31, 2009	Mar. 31, 2009
<b>Study Procedure</b>				
Animal receipt, Body weight measurement	[REDACTED]	Oct. 22, 2008	Oct. 22, 2008	Oct. 22, 2008
Stability analysis of the test substance	[REDACTED]	Oct. 23, 2008	Oct. 23, 2008	Oct. 23, 2008
Preparation of the dosing solutions	[REDACTED]	Oct. 27, 2008	Oct. 27, 2008	Oct. 27, 2008
Concentration analysis of dosing solutions	[REDACTED]	Oct. 27, 2008	Oct. 27, 2008	Oct. 27, 2008
Administration, Clinical observation	[REDACTED]	Oct. 28, 2008	Oct. 28, 2008	Oct. 28, 2008
Detailed clinical observations	[REDACTED]	Nov. 10, 2008	Nov. 10, 2008	Nov. 10, 2008
Necropsy, Organ weight measurements	[REDACTED]	Nov. 25, 2008	Nov. 25, 2008	Nov. 25, 2008
Hematological examination	[REDACTED]	Nov. 25, 2008	Nov. 25, 2008	Nov. 25, 2008
Histopathological examination	[REDACTED]	Dec. 03, 2008	Dec. 03, 2008	Dec. 03, 2008
Histopathological examination	[REDACTED]	Dec. 17, 2008	Dec. 17, 2008	Dec. 17, 2008
Shipment of the specimen	[REDACTED]	Jan. 19, 2009	Jan. 19, 2009	Jan. 19, 2009

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Inspection	Inspector	Inspection Date	Reporting Date to the Study Director	Reporting Date to the Management
Raw Data, Final Report				
Raw Data, Draft Report	[REDACTED]	Feb. 25, 2009 – Feb. 27, 2009	Feb. 27, 2009	Feb. 27, 2009
(Re-inspection)	C B I	Mar. 6, 2009	Mar. 6, 2009	Mar. 6, 2009
Raw Data, Final Report		Apr. 2, 2009	Apr. 2, 2009	Apr. 2, 2009

Quality Assurance Manager:

C B I

Date: April 2, 2009

C B I

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